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# AMERICAN JOURNAL
## OF
# OPHTHALMOLOGY

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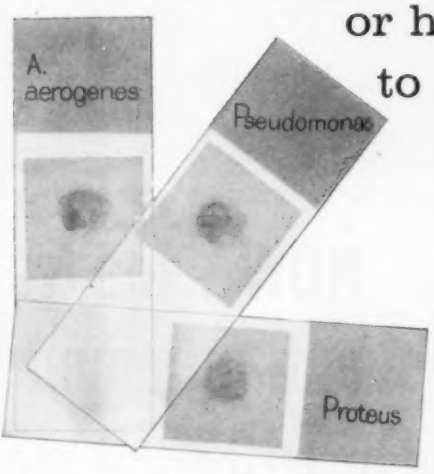


1. Department of Clinical Investigation, Lederle Laboratories, F. M. Phillips, Director. Interim Report on Clinical and Pharmacologic Investigations. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A.; Kunin, C. M., and Finland, M.: **München. med. Wchnschr.** To be published. 4. Roberts, M. S.; Seneca, H., and Lattimer, J. K.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 5. Vineyard, J. P.; Hogan, J., and Sanford, J. P.: **Ibid.**

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1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.

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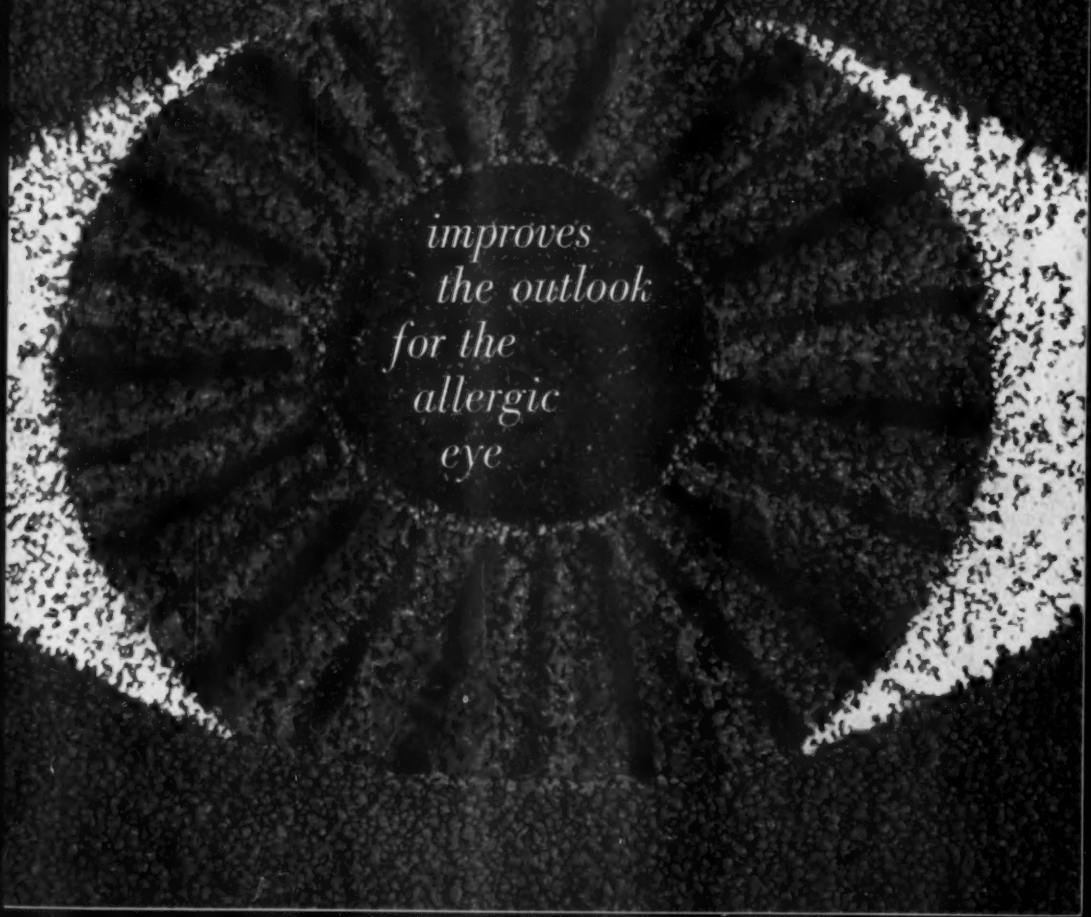

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(1) Gordon, D. M.: Am. J. Ophth. 47:536, 4/1959 • (2) Baker, W. B.: Aspects of Several Antibiotics, Drug & Cosmetic Industry, 12/1954

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[1] Girard, L. J., Dukes, C. D., and Fleming, T. C. Presented at the International Congress of Ophth., Brussels, Belgium, 1958.
[2] Kara, Gerald B., "The Use of Alpha-Chymotrypsin in Cataract Extraction," Research Report No. 10, Alcon Laboratories, Inc., 1959.
[3] Vail, D., et. al, Report: Committee on use of alpha-chymotrypsin in ophthalmology. Presented at the Sixty-fourth Annual Session, American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 11-16, 1959. (To be published)

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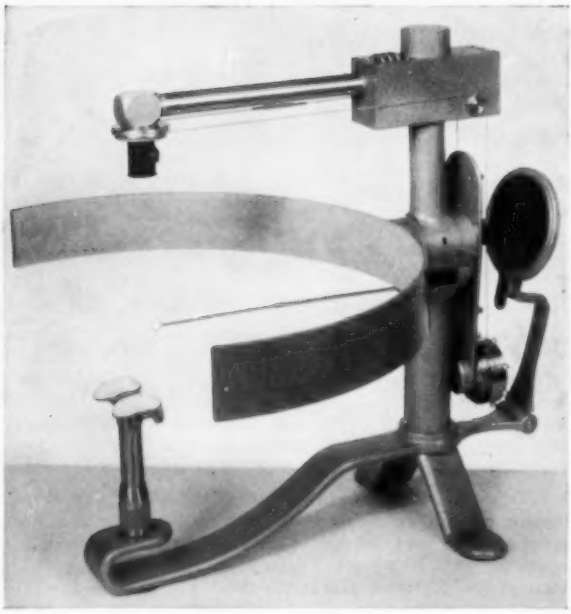

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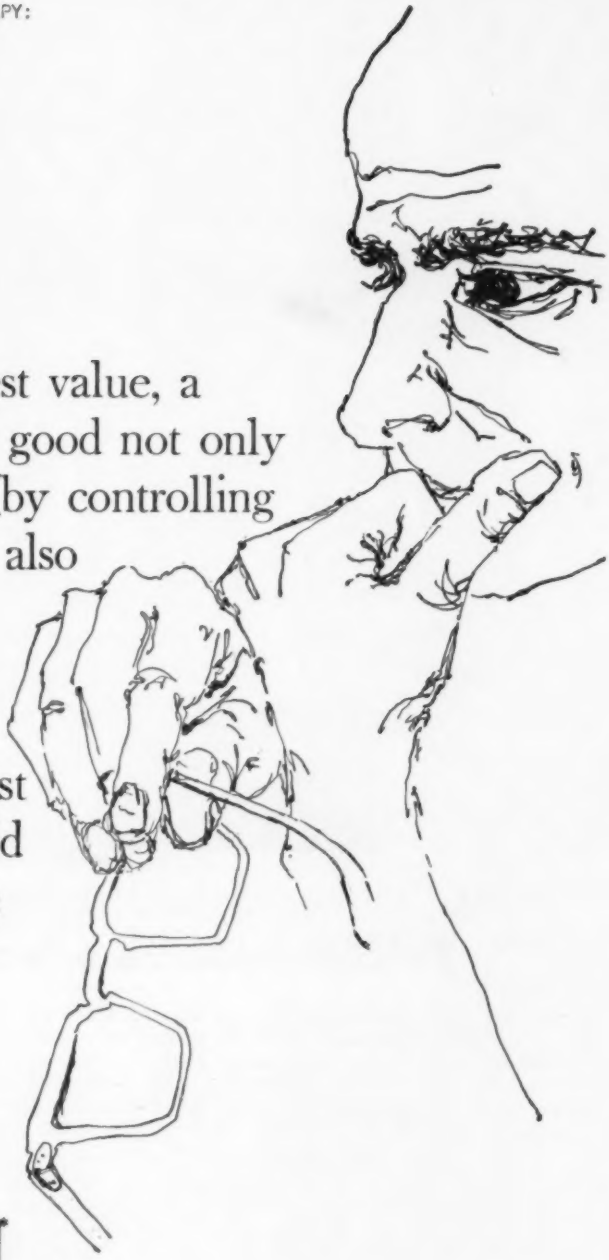

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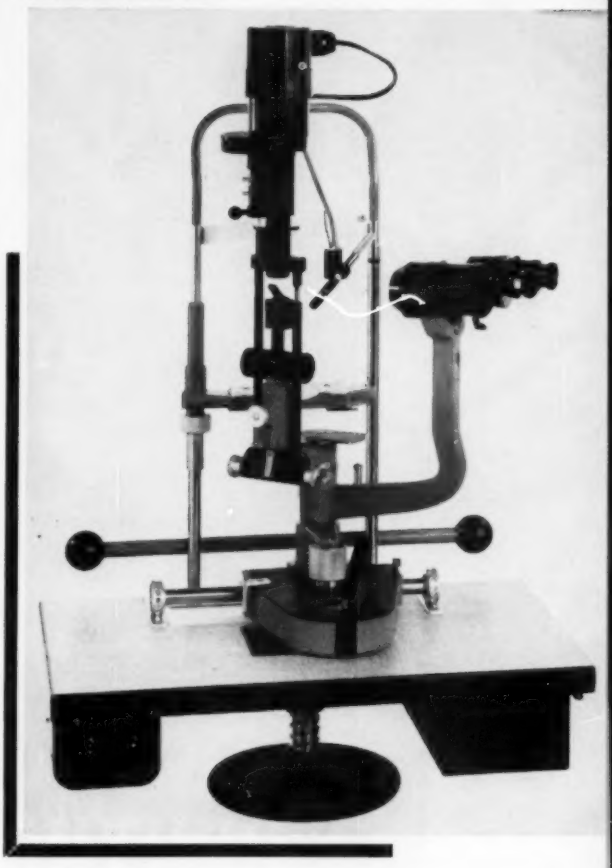

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1. Cogan, J. E. H.: Proc. Roy. Soc. Med. 51:927, 1958. 2. Jenkins, B. H.: J.M.A. Georgia 45:431, 1956. 3. Raiford, M. B.: J.M.A. Georgia 48:163, 1959. 4. Rizzuti, A. B.: A.M.A. Arch. Ophth. 61:135, 1959.

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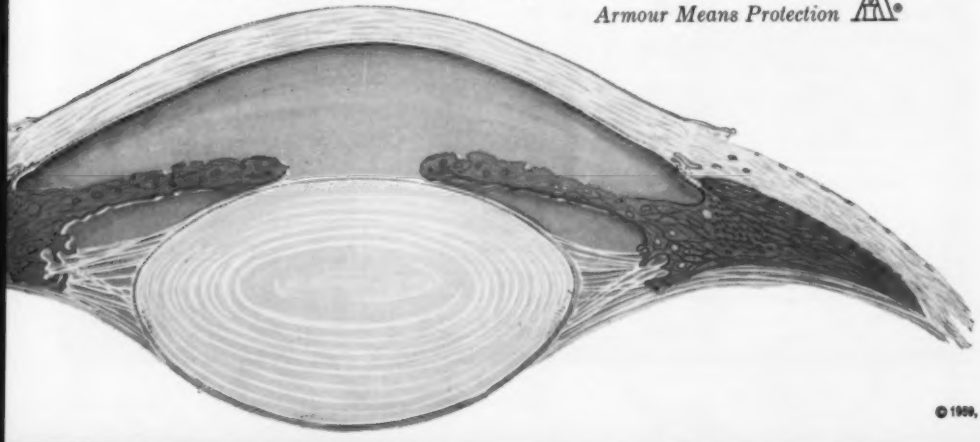

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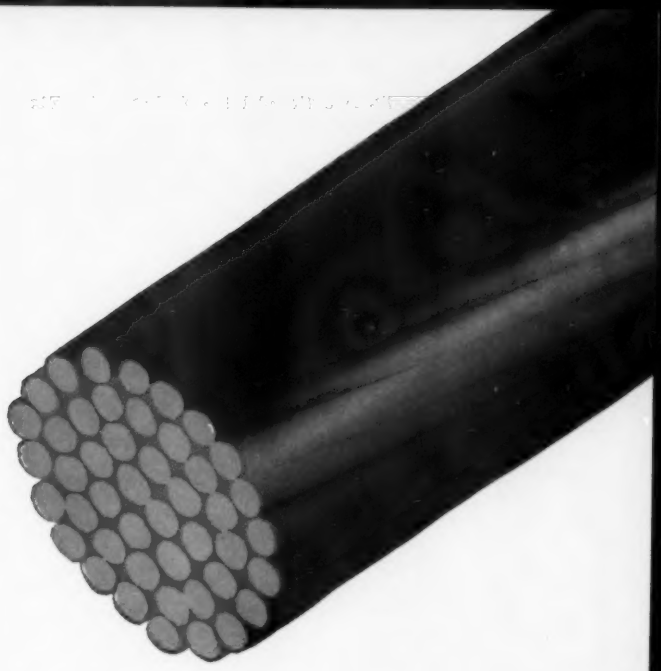

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[1] CLIFTON, C. E. AND HALL, N. C. "RE-STERILIZING ACTIVITY OF CERTAIN CONTACT LENS SOLUTIONS." CONTACTO. THE CONTACT LENS JOURNAL. 3:10, 201-2, 1959.

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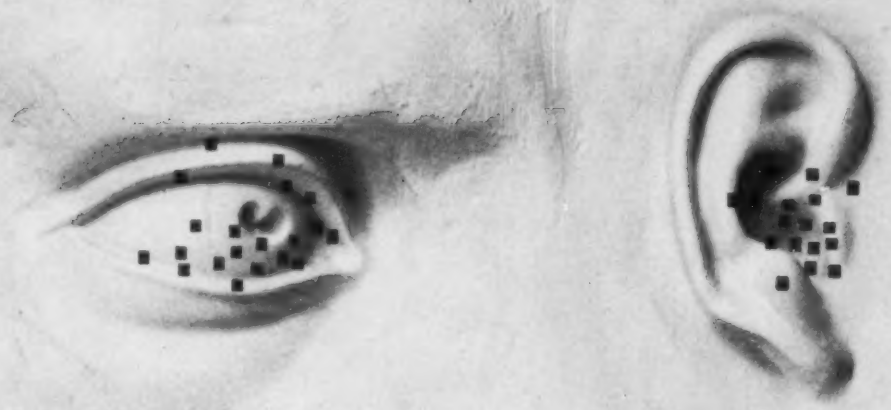

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*Baer, R. L., and Witten, V. H.: Editorial Comment. *In* The Year Book of Dermatology and Syphilology (1958-1959 Year Book Series), Edited by Rudolph L. Baer and Victor H. Witten, Chicago, The Year Book Publishers, 1959, p. 40.

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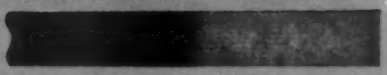

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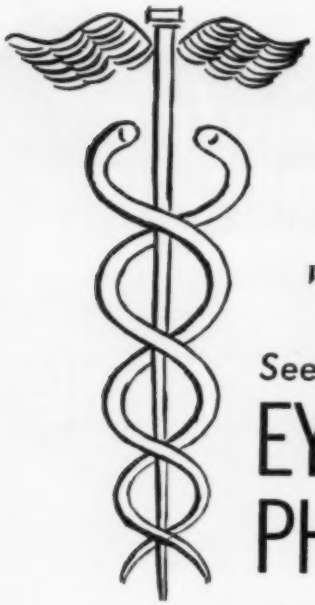

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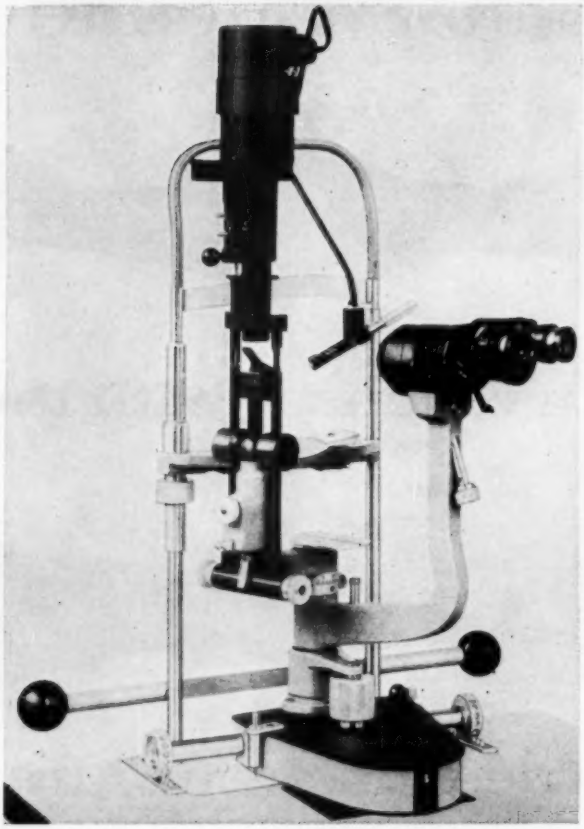

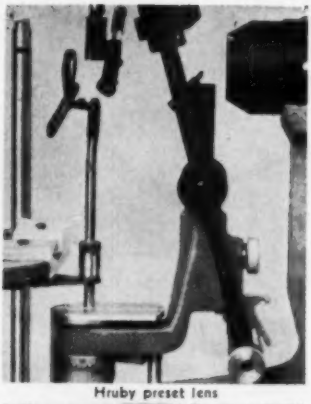

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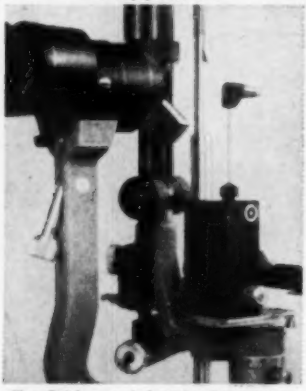

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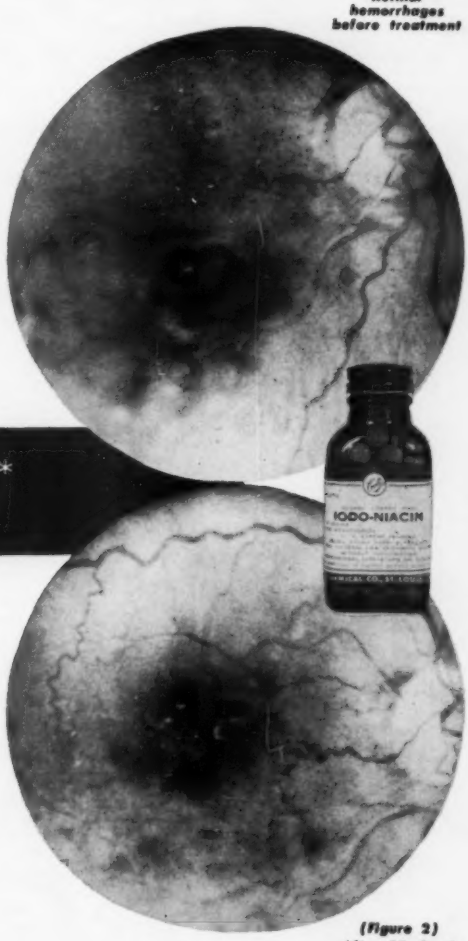
# retinal hemorrhages absorbed

*with use of*

# IODO-NIACIN*

(Figure 1)
Retinal hemorrhages before treatment




(Figure 2)
After 18 days' treatment with Iodo-Niacin

## NO IODISM

As shown by retinal photography, rapid absorption of retinal hemorrhages follows use of IODO-NIACIN. These results have been established in a series of 22 cases, 12 of retinal and 10 of vitreous hemorrhages.[1]

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1. *Am. J. Ophth.* 42:771, 1956.
2. *Am. J. Digest Dis.* 22:5, 1955.
3. *Med. Times* 84:741, 1956.

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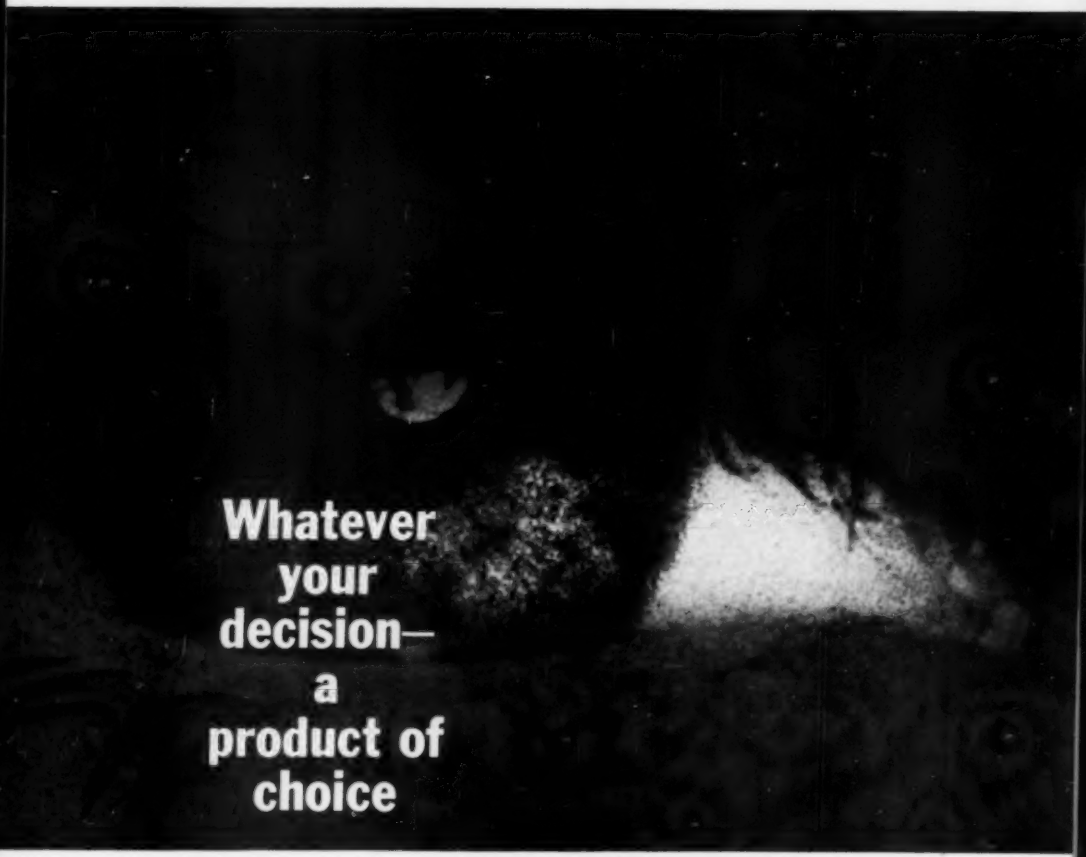

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|---|---|---|---|---|---|---|---|---|
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| 13" | 8.4" | 10.3" | 12.3" | 17.2" | 19.2" | 21.2" | 23.2" | 25.1" |
| 16" | 10.1" | 12.5" | 14.9" | 20.9" | 23.3" | 25.7" | 28.1" | 30.5" |
| 20" | 12.5" | 15.4" | 18.4" | 25.8" | 28.7" | 31.7" | 34.7" | 37.6" |

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| March 15-16-17 | March 18 | Salt Lake City, Utah | Utah |
| March 22-23-24 | March 25 | New York, New York | ‡Vision Center |
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*‡This Seminar will be held at the Wesley/Jessen Contact Lens Company, Vision Building, 635 Madison Ave., New York 22, N.Y.*

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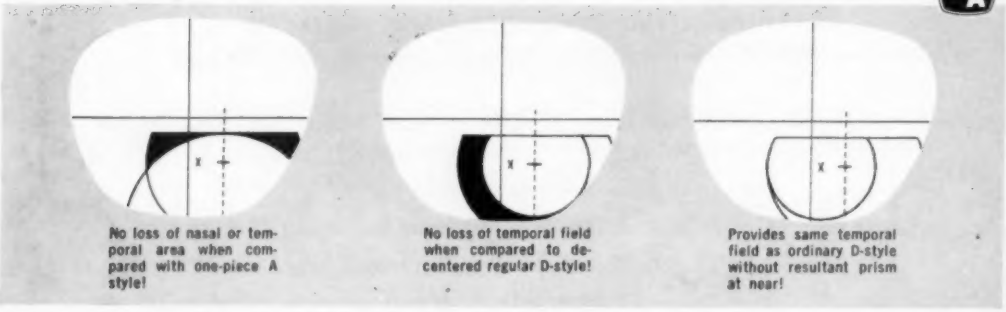
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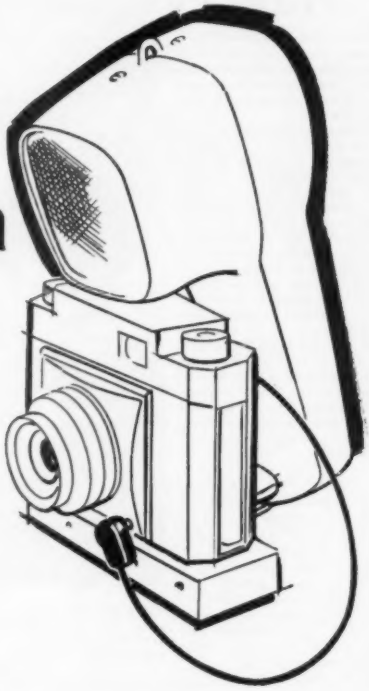

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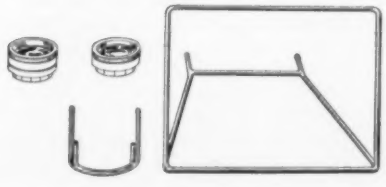


6313

**Beecher Teacher Says**

# New Eye-Testing Device More Effective

By Kenneth B. Moore, Jr.

A new eye testing machine being used by Beecher School District may reduce to memory the conventional wall-chart method.

Who doesn't remember toeing the line, covering one eye and staring hopefully at the tiny letters on the last line of a well-worn eye chart at least once during his school days?

The wall-chart test is still being used in many school systems but the Flushing Lions Club has made it possible for County schools outside Flint to put into practice the most modern method available for eye-testing.

The club presented the machine to Flushing schools, which are making it available to any County school system which wants to use it. The Beecher district was the first, and the Flushing district will use it next.

* * *

This reporter stopped at Buick Elementary School in the Beecher district to see how the device operates.

Mrs. Donald L. Esmond, a Beecher teacher trained by the Michigan Department of Health to conduct the tests, welcomed the reporter and asked him to run through the tests given to pupils.

After sitting in front of the machine, the reporter peered through a viewer and did the following: Told Mrs. Esmond where a little electronic "red apple" appeared on a view-slide of a picnic table: called out a couple of lines of letters on two other slides and asked the technician how he'd done.

Mrs. Esmond explained the results of the test and these added up to: "You flunk."

Seems that this reporter, according to the tests, is far sighted and has muscle imbalance.

Mrs. Esmond said that the "apple" test shows whether eyes are working together in proper balance.

"You positioned the apple in a spot which reflects muscle imbalance," she said.

The parents of children who are found to be farsighted or nearsighted or who have muscle imbalance are notified after a second test bears out the original findings.

Mrs. Esmond said the device is simple to operate and highly accurate.

So far at Beecher, 218 children of 2,066 checked have failed in the testing. There are 127 other possible failures.

Mrs. Esmond said that the machine is more effective than wall charts because it can detect more possible eye defects. The charts are mainly effective in detecting nearsightedness.

"There is no chance that children waiting in line can memorize the chart before it is their turn to take the test, either," Mrs. Esmond added.

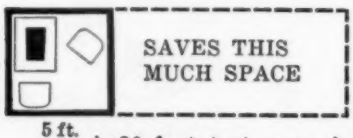
Mrs. Esmond said that doing the testing is a "wonderful and rewarding experience" and that she hopes other County schools will take advantage of the opportunity to use the device.

(Journal Photo)

EYES RIGHT—A new machine, the first of its kind to be used in Genesee County schools, is operated by Mrs. Donald L. Esmond, technician for Beecher School District, to test the vision of Jay Young, 10, G-6161 N. Saginaw Rd. Mrs. Esmond said the machine, made by Titmus Optical Co., Petersburg, Va., is being used by many schools in other Michigan counties.

Reprinted from The Flint Journal, Flint, Mich.


# T/O SCHOOL VISION TESTER

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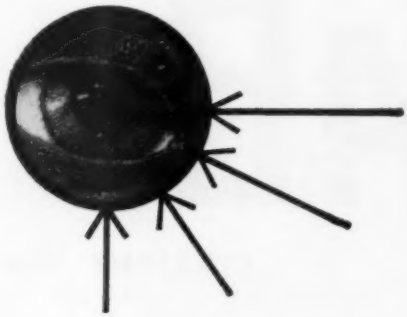

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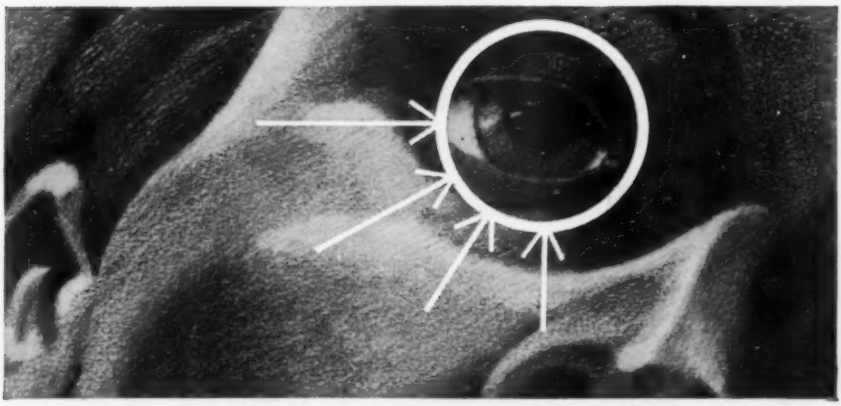

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# SINGLE VISION DECENTRATION

Many good refractions have been nullified by incorrectly centered lenses. While this is especially true of bifocal lenses, it is also true of single vision lenses.

To illustrate the importance of correct decentration, we present the case of Mr. O.

Mr. O. had been employed in a capacity that called for little or no close work. He was not presbyopic and his distance correction was approximately O.U.: +2.50 +0.50 x 90. This correction had been worn comfortably for several years. His work was changed to a position that required a lot of close work which he was not able to do successfully because his eyes tired. He was refracted again and his correction was found to be almost exactly what he was wearing.

A check of his lenses revealed that they were properly centered for distance and, therefore, were not correctly centered for near. The eyes converge for near and in this case, Mr. O. was forced to overcome 1.2 prism diopters of base out prism when working at close range. Decentering each lens in two millimeters was all that was necessary to give Mr. O. complete comfort.

A safe rule for centering single vision lenses is as follows: center all minus prescriptions at the distance P.D.; center all plus prescriptions either at the near P.D. or at an intermediate P.D. This rule works because the myope centered for distance has a little base in prism for near which will not hurt him. The hyperope centered at the near P.D. gets a little base in prism at the distance which also will do no harm. Of course, in very strong corrections, minus or plus six diopters or more, two pairs of glasses may be necessary—one pair centered for distance and one for near. Below six diopters the rule will be found very helpful.

*"if it's a lens problem, let's look at it together"*

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SERIES 3 · VOLUME 49 · NUMBER 4 · APRIL, 1960

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VOLUME 49 APRIL, 1960 NUMBER 4

# THE EFFECT OF PARALYSIS OF THE CERVICAL SYMPATHETIC SYSTEM ON THE ELECTROMYOGRAM OF EXTRAOCULAR MUSCLES IN THE HUMAN*

## WITH PARTICULAR REFERENCE TO THE STRIATED LEVATOR IN HORNER'S SYNDROME

FREDERICK C. BLODI, M.D., AND MAURICE W. VAN ALLEN, M.D.
*Iowa City, Iowa*

The question whether the autonomic nervous system in general and the sympathetic system in particular mediate any influence on the contraction of extraocular muscles has recently been debated. Histologic examinations of nerve fibers and nerve endings in the extraocular muscles have been meticulous and detailed, but interpretations of the findings have been at variance. It has been claimed that the nonmedullated nerve fibers of the extraocular muscles are autonomic fibers stemming either from the sympathetic system of the vascular plexuses or from the parasympathetic fibers of the third cranial nerve.[1] These claims have not been substantiated and several other functions have been ascribed to these nonmedullated fibers.[2]

In recently reported studies on cats no change in the state of the extraocular muscles occurred when the superior cervical ganglion was stimulated.[3] However, the structure of the autonomic nervous system and the muscle of the cat are not entirely comparable to that of man.

We postulated that a study of the electromyogram of human extraocular muscles following stellate ganglion block or in cases of naturally occurring sympathetic paralysis (Horner's syndrome) might help to elucidate the role of the sympathetic nervous system in the contraction and "tone" of these muscles.

### METHOD

The technique of obtaining and recording the electromyogram was identical to that described previously.[4]

The stellate-ganglion block was done in a routine manner with infiltration by procaine solution. Only after unequivocal ipsilateral miosis and ptosis appeared was the study continued.

Recordings were taken before the block so that a stable baseline was established. The electromyogram in strong and weak contraction was recorded and the baseline of reference was that degree of activity evident with the patient in a relaxed position and fixing his gaze on a point straight ahead, approximately 10 feet away. The recordings were repeated after the block at 10-minute intervals for at least an hour or until the visible effects of the block had practically disappeared. The needle remained fixed and unchanged during the entire procedure with only occasional minor adjustments.

### MATERIAL

1. Eight patients were examined in this way before, during, and after cervical sympathetic paralysis effected by stellate ganglion block. The medical indication for the block was vascular insufficiency or disease

* From the Services of Ophthalmology and Neurology, Veterans Administration Hospital, Iowa City, and the Departments of Ophthalmology and Neurology, State University of Iowa. This paper was presented at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959.

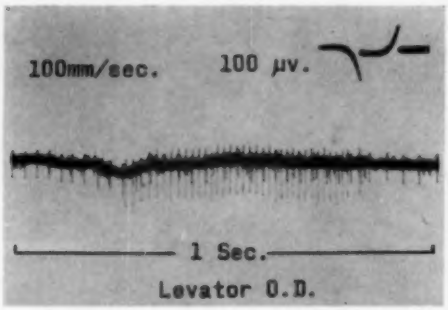


Fig. 1 (Blodi and Van Allen). Electromyogram of the right levator muscle in a diabetic patient with third-nerve paresis, exhibiting the neuropathic pattern.

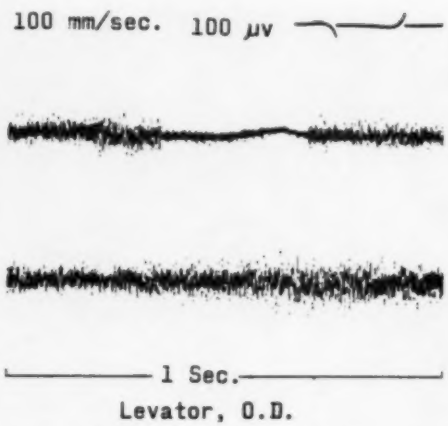


Fig. 2 (Blodi and Van Allen). Electromyogram of the right levator muscle in a patient with thyrotoxic ophthalmoplegia, exhibiting the myopathic pattern.

of the brain or arm, retinitis pigmentosa, or retrobulbar neuritis. In six of these patients the levator of the upper lid was tested and in the other two patients recordings were taken from the internal rectus muscle. The levator muscle was most frequently tested because it is in the range of action of this muscle that the effects of sympathetic paralysis are most conspicuous. It was anticipated that if the block had any influence on the ac-

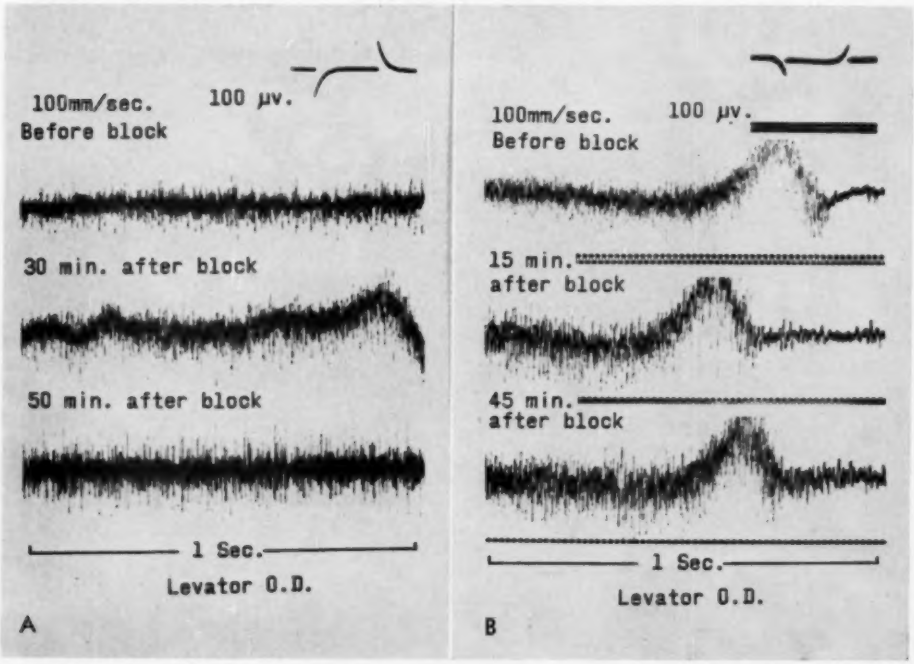


Fig. 3 (Blodi and Van Allen). (A) Electromyogram of a right levator muscle at rest before and during sympathetic paralysis by cervical sympathetic block. (B) Electromyogram of a right levator muscle of another patient at maximal activity before and during cervical sympathetic block.

tion of extraocular muscles, that such influence might be more easily detected in the striated levator than in another extraocular muscle.

2. Two patients with long-standing, unilateral Horner's syndrome were also tested. One of these was a 41-year-old man who had a left-sided Horner's syndrome since childhood. His history suggested encephalitis in childhood. It was thought that the Horner's syndrome was of central origin. The other was a 28-year-old man in whom right-sided ptosis and miosis had appeared following thrombosis of the anterior spinal artery four months before. In these two patients recordings were taken simultaneously from the levator muscles of both eyes. In this way the normal muscle could be compared with the muscle which had presumably been deprived of sympathetic innervation for months or years.

3. For comparison, recordings were obtained from several of the patients with ptosis of known etiology other than sympathetic denervation. Two typical examples are presented. In the first patient, a diabetic, the ptosis was associated with other signs of paresis of the third nerve. The electromyographic pattern showed few potentials firing irregularly in a manner characteristic of a neurogenic lesion (fig. 1).

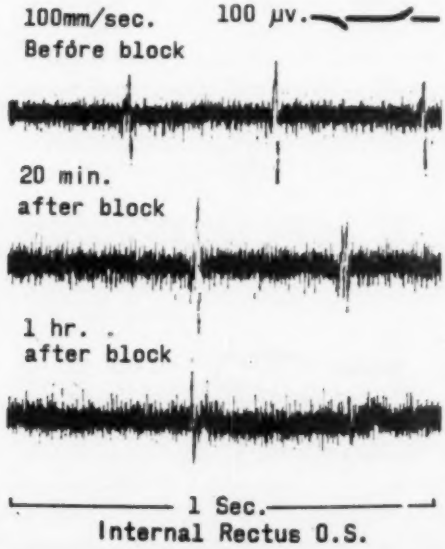


Fig. 4 (Blodi and Van Allen). Electromyogram of a left internal rectus at rest before, during, and after the effects of a cervical sympathetic block.

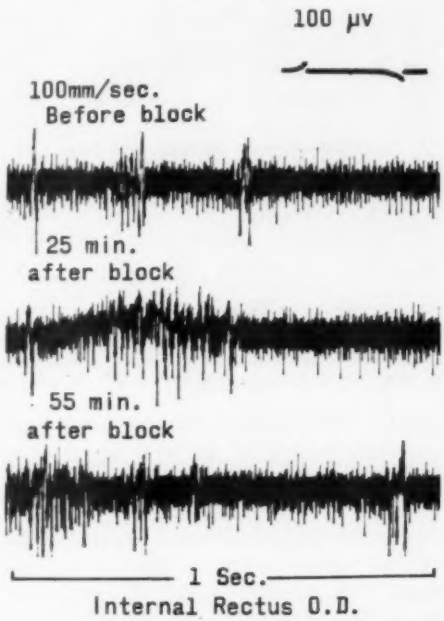


Fig. 5 (Blodi and Van Allen). Electromyogram of a right internal rectus during convergence before, during, and after a cervical sympathetic block.

The second patient showed a severe thyrotoxic ophthalmoplegia. He will be described more extensively elsewhere,[5] but recordings from his levator muscle show numerous potentials of small amplitude typical of a myopathic pattern (fig. 2).

## Results

1. Induced paralysis of the cervical sympathetic system produced no consistent effect on the electrical activity of the levator muscle. Minor changes could be observed only during the first 20 minutes after the injection while the visible effects of the block lasted at least twice as long. These changes consisted of a small decrease of total electrical activity in two patients and of a small increase of the electrical activity in two other

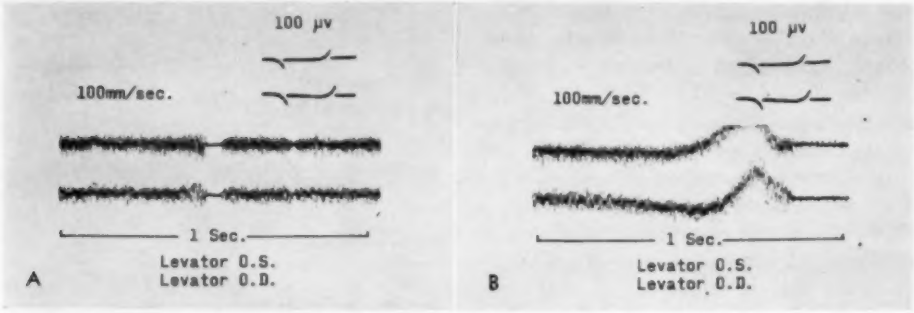


Fig. 6 (Blodi and Van Allen). Simultaneous recording of both levator muscles in a patient with spontaneous right-sided Horner's syndrome secondary to thrombosis of the anterior cervical artery. (A) At rest. (B) At maximal activity.

patients. In the remaining two patients no detectable change in the level of electrical activity occurred (Fig. 3).

2. The stellate ganglion block did not change the level of electrical activity of the internal rectus muscles in the two patients tested (fig. 4). Neither did it seem to influence the electrical activity of this muscle on command convergence (fig. 5).

3. In two patients with long-standing Horner's syndrome simultaneous recordings from the two levator muscles did not reveal any appreciable difference in electrical activity between the affected and the normal eye (fig. 6). In the patient with a Horner's syndrome of many years standing, there was at times during the recording a suggestion of decreased electrical activity of the levator muscle on the affected side (fig. 7).

## Comments and Conclusions

1. Paralysis of the cervical sympathetic system by stellate-ganglion block did not significantly influence the electrical activity of ipsilateral levator muscle. Minor variations were inconsistent and were in no correlation with the visible effects of the block. Even when ptosis was marked, the electrical activity of the striated levator was not detectably less than that before block was established. It can therefore be concluded that the sympathetic system does not measurably contribute to the innervation of the striated levator muscle.

2. Simultaneous recordings of the activity of the two levator muscles were taken from two patients with long-standing, unilateral Horner's syndrome. There was no difference in the electrical activity between the normal

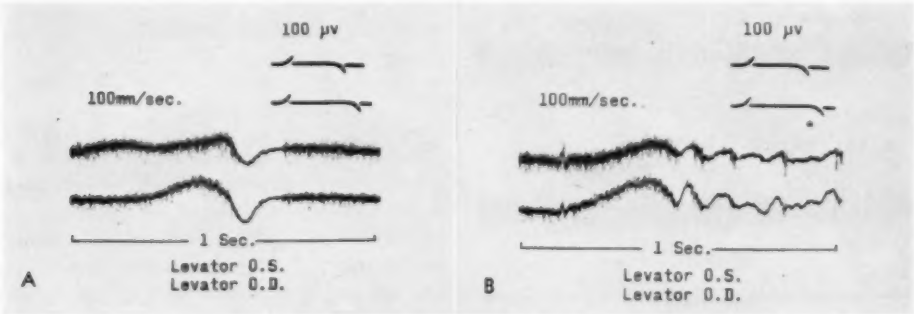


Fig. 7 (Blodi and Van Allen). Simultaneous recording of both levator muscles in a patient with a right-sided Horner's syndrome of many years' standing. (A) At rest with blink-reflex. (B) Looking downward.

and the affected eye in one patient and only minor differences in the other.

3. A stellate-ganglion block did not influence the electrical activity of the internal rectus muscle of two patients. There was no appreciable change on command convergence. This is especially interesting as an autonomic nervous control for vergence movements has been postulated.[6] On the basis of our studies it seems unlikely that such control is exerted via the sympathetic system.

*University Hospitals.*


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# CLINICAL ORBITONOMETRY*

## IN THE PROGRESS AND TREATMENT OF GRAVES' OPHTHALMOPATHY


ADOLFO GÓMEZ MORALES, M.D., ALBERTO FERRER ARATA, M.D., AND JUAN REFORZO MEMBRIVES, M.D.

*Buenos Aires, Argentina*


Orbitonometry is a procedure which permits the measurement of exophthalmos and of the orbital tension with sufficient accuracy. Both of these criteria might be of great value in appreciating the evolution of the ophthalmopathy which accompanies Graves' disease and in estimating the response to any therapy. The purpose of this paper is to present and discuss the results obtained by serial orbitonometric examinations of a series of patients with Graves' disease and ophthalmopathy who received different treatments.

### MATERIAL

The material is composed of 50 patients with different grades of thyrotoxicosis and ophthalmopathy.

We classify thyrotoxicosis conventionally in four grades according to basal metabolism, cardiovascular condition and neuromuscular condition, as shown in Table 1.

We also classify ophthalmopathy in four grades according to the level of exophthalmos, orbital tension, palpebral retraction, palpebral edema and the involvement of the extrinsic muscles, as explained in Table 2. Since ophthalmopathy of Graves' disease represents a polymorphous and evolving condition, this classification is absolutely conventional as all the others (Brain,[1] Mann,[2] Kearns and Henderson,[3] Barraquer[4]), designed to differentiate isolated types and grades in the so-called endocrine exophthalmos. The classification we have established has been useful in conceiving an approximate ophthalmopathic pattern based on a simple sign.

The 50 patients we have observed are distributed according to the grade of thyrotoxi-

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* From the Santa Lucia Ophthalmological Hospital and the Clinic of Endocrinology and Metabolism, Buenos Aires.

TABLE 1

CHARACTERISTICS OF THE FOUR GRADES OF THYROTOXICOSIS

| | |
|---|---|
| Grade 1 | Basal metabolic rate: up to +20<br>Cardiovascular condition: light<br>Neuromuscular condition: light |
| Grade 2 | Basal metabolic rate: up to +40<br>Cardiovascular condition: moderate<br>Neuromuscular condition: moderate |
| Grade 3 | Basal metabolic rate: up to +70<br>Cardiovascular condition: marked<br>Neurovascular condition: marked |
| Grade 4 | Basal metabolic rate: more than +70<br>Cardiovascular condition: extreme<br>Neurovascular condition: extreme |

cosis and ophthalmopathy, as indicated in Figure 1.

## METHOD

The evaluation of the intensity of the cardiovascular and neuromuscular condition was a subjective one. The basal metabolic rate was determined by indirect respiratory calorimetry with an apparatus of the Benedict-Roth type.

Three of the five features we distinguish in ophthalmopathy, namely palpebral retraction, palpebral edema and the involvement of the extraocular muscles, have been evaluated exclusively in a subjective form. The other two features—exophthalmos level and orbital tension—have been measured with Copper's orbitonometer[5] (fig. 2), already described in a former paper.[6]

We also present a diagram (fig. 3) showing the results of the orbitonometric measurements on 450 patients without orbital diseases, and which includes a statistically significant majority of physiologic orbitonometric values, that permits one to establish in each particular case whether it agrees with the majority or whether it differs significatively.

It must be kept in mind that the absolute orbitonometric value (Eo) represents the

TABLE 2

CHARACTERISTICS OF THE FOUR GRADES OF OPHTHALMOPATHIES

| | |
|---|---|
| Grade 1 | Exophthalmos: 20 mm. or less with less than 2 mm. difference between both eyes<br>Orbital tension: normal<br>Palpebral retraction: moderate<br>Palpebral edema: negative<br>Involvement of extrinsic muscles: negative |
| Grade 2 | Exophthalmos: between 20.5 and 25 mm. or 2 to 3 mm. difference between both eyes<br>Orbital tension: normal or slightly increased<br>Palpebral retraction: marked or moderate<br>Palpebral edema: negative or moderate<br>Muscular involvement: negative or moderate |
| Grade 3 | Exophthalmos: between 25.5 and 30 mm. or more than 3 mm. difference between both eyes<br>Orbital tension: markedly increased<br>Palpebral retraction: marked or moderate<br>Palpebral edema: marked, moderate or negative<br>Muscular involvement: moderate, marked or negative |
| Grade 4 | Exophthalmos: more than 30 mm. with ocular or corneal complications, etc.<br>Orbital tension: extremely increased<br>Palpebral retraction: marked<br>Palpebral edema: marked or extreme<br>Muscular involvement: marked or extreme |

degree of exophthalmos, and that relative orbitonometric value (Y4)—the result of the difference (E4-Eo)—represents the degree of the tension. We have not considered the form of the curve which expresses the distribution of the tension along the orbit,[7] and the variations of which we do not believe to be very useful in the examinations of endocrine ophthalmopathies.

Copper finds a correlation between the prominence of the eyes and the orbital tension in his series of 60 normal adults, as shown in Table 3. As a consequence of this physiologic correlation, the evaluation of orbital tension has always to be referred to the exophthalmos level. Therefore, we have classified the orbital tension as normal, slightly increased, markedly increased, and extremely increased, according to the following criteria:

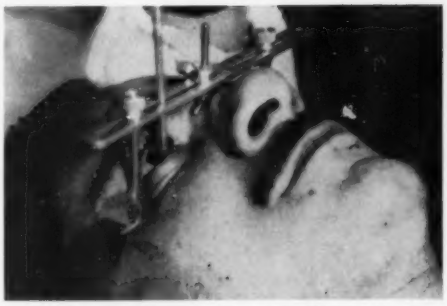


Fig. 2 (Gómez, Ferrer and Reforzo). Instrument in position.

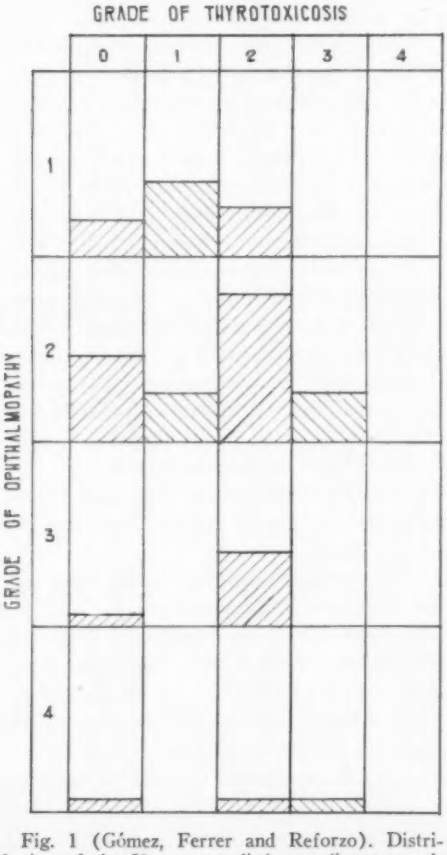
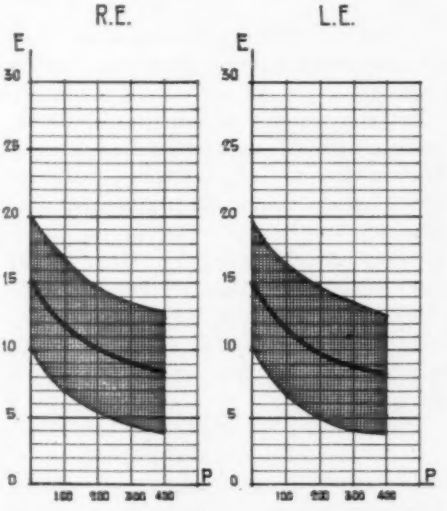



Fig. 1 (Gómez, Ferrer and Reforzo). Distribution of the 50 cases studied according to grade of thyrotoxicosis and grade of ophthalmopathy.




| G | VALUES OF E | MARGIN OF ERROR 95% |
|---|---|---|
| 2.480 | Eo = 15.21 | 20.07 |
| | | 10.36 |
| 2.535 | E1 = 11.67 | 16.83 |
| | | 6.51 |
| 2.380 | E2 = 10.11 | 14.77 |
| | | 5.45 |
| 2.562 | E3 = 9.13 | 13.78 |
| | | 4.48 |
| 2.683 | E4 = 8.42 | 12.99 |
| | | 3.86 |

| G | VALUES OF E | MARGIN OF ERROR 95% |
|---|---|---|
| 2.586 | Eo = 14.91 | 19.58 |
| | | 10.24 |
| 2.486 | E1 = 11.60 | 15.46 |
| | | 6.74 |
| 2.512 | E2 = 9.87 | 14.79 |
| | | 4.95 |
| 2.462 | E3 = 8.85 | 13.74 |
| | | 4.08 |
| 2.380 | E4 = 8.24 | 12.66 |
| | | 3.82 |

Fig. 3 (Gómez, Ferrer and Reforzo). Results of orbitonometric measurements on 450 patients without orbital diseases.

TABLE 3

CORRELATION BETWEEN PROMINENCE OF EYES AND ORBITAL TENSION

| (mm.) | (mm.) | |
|---|---|---|
| Eo = 12.0 : | $Y_4$ = 6.0 | ±1.5 mm. |
| Eo = 14.0 : | $Y_4$ = 7.0 | |
| Eo = 16.0 : | $Y_4$ = 7.5 | |
| Eo = 18.0 : | $Y_4$ = 8.0 | |
| Eo = 20.0 : | $Y_4$ = 8.5 | |
| Eo = 24.0 : | $Y_4$ = 9.0 | |
| (copper) | | |

a. The orbital tension is *normal* when (Y4) is less than 1.5 mm. below the average normal value corresponding to the correlated exophthalmos level (Eo) obtained.

b. The tension is *slightly increased* when (Y4) is from 1.5 to 2.5 mm. below the corresponding average normal value.

c. It is *markedly increased* when it is from 2.5 to 4.0 mm. below the average normal value.

d. And it is *extremely increased* when it is more than 4.0 mm. below the average normal value.

For instance, if a patient examined orbitonometrically has an exophthalmos level of 20 and a value of (Y4) of 7.5, we consider his orbital tension as normal, because the same decreases less than 1.5 mm. of the corresponding physiologic average which, in this case, would be 8.5 mm.; being the value (Y4), in the same case, 6.5, we should consider the orbital tension as slightly increased, as it decreases 2.0 mm. of the physiologic average.

The following treatments have been tried:

1. *Antithyroid drugs*, among which we include methyl-mercaptoimidazole in a dosage that varies between two and eight tablets of 5.0 mg. each of active substance, and, propylthiouracil in a dosage of two to eight capsules of 50 mg. each.

2. *Lugol's solution*, in a dosage of five to 10 drops a day.

3. *Subtotal thyroidectomy.*

4. *Thyroid*, in form of dried powder, in tablets of 65 mg., one-half to two tablets a day.

5. *Acetazolamide*, tablets of 250 mg., one to three tablets a day.

6. *Corticotropin.* Gel of ACTH, intramuscular injections of one cc. (20 μ.) every 12 hours, for 10 days.

7. *Hyaluronidase*, one vial of 150 t.r.u. dissolved in one cc. of five-percent Novocaine administered by retrobulbar injection.

8. *Hydrocortisone acetate*, 0.25 cc. of a solution of 25 mg. per cc. administered by retrobulbar injection.

9. *Testosterone*, weekly intramuscular injection of 2.0 cc. of an aqueous suspension of microcrystals that contains 25 mg. per cc.

10. *Radiotherapy of the orbit*, 500 r in 10 applications of 50 r every three days.

11. *Radiotherapy of the pituitary gland*, 1,500 r in a dosage of 150 r per session, every three days.*

We have only taken into consideration the effects of the different treatments on ophthalmopathy, without considering the modifications produced by them on the other components of Graves' disease which do not form part of this paper, even more as the orbital disease and thyrotoxicosis do not develop always in the same way.

The improvement or aggravation of the ophthalmopathy has been evaluated, especially as to the variations of exophthalmos and orbital tension, by the objective means of orbitonometric examination. The intensity of the improvement or aggravation has been classified into three different grades, according to the following criteria:

a. The mean level of exophthalmos during the course of time of a certain treatment is established.

b. The mean tension during the same period of time is also established.

c. Both values are compared with the mean values of the corneal level and orbital tension before instituting the treatment.

According to this, the improvement or aggravation is considered to be 0, +, ++, −, −−, as the exophthalmos and/or the ten-

* Radiotherapy was under the direction of Lanari Eduardo, M.D., the National Institute of Radiology and Physiotherapy, whom we wish to thank for his collaboration.

TABLE 4

FINDINGS IN 50 PATIENTS EXAMINED

| Case | Sex | Age (yr.) | Grade of Thyrotoxicosis | Grade of Ophthalmopathy | Antithyroid Drugs | Lugol's Solution | Thyroidectomy | Thyroid | Acetazolamide | Corticotropin | Retrobulbar Vortisone | Retrobulbar Hyaluronidase | Testosterone | Radiotherapy of Orbit | Radiotherapy of Pituitary Gland |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 17 | 3 | 2 | 0 | | | 0 | 0 | 0 | | 0 | 0 | $0^{E+}$ | + |
| 2 | M | 42 | 2 | 2 | − | | | 0 | $0^{E+R+}$ | | | | | | |
| 3 | F | 50 | 2 | 2 | 0 | | | 0 | | 0 | | 0 | 0 | $0^{E+}$ | |
| 4 | M | 60 | 0 | 3 | | | | − | | 0 | | | | | |
| 5 | M | 59 | 1 | 2 | | | | + + | 0 | 0 | − − | 0 | 0 | | |
| 6 | F | 46 | 2 | 3 | | | | 0 | | 0 | | | | | |
| 7 | M | 21 | 3 | 2 | 0 | 0 | 0 | 0 | | 0 | | | | | |
| 8 | M | 38 | 2 | 2 | | | | 0 | | | | 0 | | | |
| 9 | F | 61 | 2 | 2 | | 0 | | 0 | | 0 | − | | | | |
| 10 | M | 49 | 2 | 4 | − | | | + | | | | 0 | | | |
| 11 | F | 41 | 1 | 1 | 0 | 0 | | | | | | | | | |
| 12 | F | 53 | 2 | 3 | | | | 0 | $0^{E+}$ | 0 | | | | + | |
| 13 | F | 31 | 2 | 2 | 0 | | | | $0^{E+R+}$ | | | | | | |
| 14 | F | 36 | 2 | 2 | 0 | | | | | | | | | | |
| 15 | F | 36 | 1 | 1 | 0 | | | | | | | | | | |
| 16 | F | 40 | 0 | 2 | | | 0 | 0 | | | | | | | |
| 17 | F | 29 | 2 | 2 | | 0 | | 0 | | | | | | | |
| 18 | F | 44 | 2 | 2 | 0 | 0 | 0 | 0 | | | | | | | |
| 19 | F | 30 | 3 | 2 | 0 | | | | | | | | | | |
| 20 | M | 43 | 2 | 2 | 0 | | | 0 | | | | | | | |
| 21 | F | 31 | 2 | 3 | 0 | | | | | | | | | | |
| 22 | F | 50 | 1 | 1 | 0 | | | | | | | | | | |
| 23 | F | 30 | 0 | 1 | | | | 0 | | | | | | | |
| 24 | F | 43 | 1 | 2 | 0 | | | | | | | | | | |
| 25 | M | 48 | 2 | 3 | − | | | 0 | | 0 | | | | | |
| 26 | F | 46 | 1 | 2 | 0 | | | | | | | | | | |
| 27 | F | 20 | 0 | 2 | | | − | 0 | | | | | | | |
| 28 | F | 42 | 1 | 1 | 0 | 0 | | | | | | | | | |
| 29 | F | 40 | 2 | 1 | 0 | | | | | | | | | | |
| 30 | M | 50 | 1 | 2 | 0 | | | 0 | | | | | | | |
| 31 | F | 50 | 2 | 1 | 0 | | | | | | | | | | |
| 32 | F | 44 | 0 | 2 | 0 | | | 0 | | 0 | | | | | |
| 33 | F | 36 | 2 | 1 | 0 | | | | | | | | | | |
| 34 | M | 41 | 3 | 2 | 0 | | | | | | | | | | |
| 35 | F | 29 | 2 | 1 | − | | | | | | | | | | |
| 36 | M | 41 | 1 | 1 | 0 | | | | | | | | | | |
| 37 | F | 54 | 2 | 2 | | | | | | | | | | 0 | |
| 38 | F | 45 | 0 | 2 | | | | | $0^{E+R+}$ | | | | | | |
| 39 | F | 49 | 0 | 2 | | | + | + | | | | | | | |
| 40 | F | 43 | 0 | 1 | | | | + | | | | | | | |
| 41 | F | 50 | 2 | 3 | − | − | | | — | | | | | | |
| 42 | F | 34 | 0 | 1 | | 0 | | 0 | | | | | | | |
| 43 | F | 32 | 0 | 2 | 0 | | | 0 | | | | | | | |
| 44 | M | 35 | 2 | 2 | − | − | | | | | | | | | |
| 45 | M | 52 | 0 | 4 | − | | | | $0^{E+}$ | | | | | | |
| 46 | M | 57 | 3 | 4 | − − | | | − − | | | | | | − | − − |
| 47 | F | 48 | 1 | 1 | 0 | | | | | | | | | | |
| 48 | F | 32 | 0 | 2 | | | | 0 | 0 | | | | | | |
| 49 | F | 43 | 2 | 2 | 0 | | 0 | 0 | | | | | | 0 | |
| 50 | M | 47 | 2 | 3 | | | − − | − − | | | | | | | − |

TABLE 5

RESULTS OF VARIOUS TREATMENTS

| Results | Anti-thyroid Drugs | Lugol | Thyroid-ectomy | Thyroid | Acetazol-amide | Cortico-tropin | Retro-bulbar Cortisone | Retro-bulbar Hyalu-ronidase | Testos-terone | Radio-therapy of Orbit | Radio-therapy of Pituitary Gland |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 25 | 7 | 4 | 20 | 8 | 9 | | 4 | 2 | 4 | |
| − | 7 | 2 | 1 | 2 | 1 | | 1 | | | 1 | 3 |
| − − | 1 | | 1 | 2 | | | 1 | | | | |
| + | | | 1 | 3 | | | | | | 1 | 1 |
| + + | | | | 1 | | | | | | | |
| TOTAL | 33 | 9 | 7 | 28 | 9 | 9 | 2 | 4 | 2 | 6 | 4 |

sion have increased or decreased in the following manner:

| IMPROVEMENT | AGGRAVATION |
|---|---|
| Exophthalmos and tension decrease: | Exophthalmos and tension increase: |
| Less than 1.5:0 | Less than 1.5:0 |
| Between 1.5 and 2.5: + | Between 1.5 and 2.5: − |
| More than 2.5: + + | More than 2.5: − − |

If the components which can be measured orbitonometrically have not undergone modifications but there have been variations in the other components of the ophthalmopathy, as for instance retraction and edema of the lids, these variations are quoted as a marginal note with the corresponding sign which is of a subjective nature only.

## RESULTS

The results are presented in Tables 4 and 5.

## DISCUSSION

Of the 50 patients with Graves' disease and ophthalmopathy, presented in Table 4, 35 were women 15 men; the incidence among women seems, therefore, to be much higher than among men. This agrees with the findings of earlier investigators (80 to 90 percent).

There have been many attempts to divide Graves' ophthalmopathy into two separate clinical entities (Brain,[8] Mulvany,[9])—the classic, thyrotoxic, palpebral retraction type and the paradoxic, thyrotropic, ophthalmoplegic or edematous type of exophthalmos, attributing to each one of these two types a well-recognized clinical picture (table 6). It has also been stated that there exist differences as to the age and sex between one type of exophthalmos and the other, the retractopalpebral type being more characteristic of young women and the edematous ophthalmoplegic type more frequent in older men.

TABLE 6

TYPES OF OPHTHALMOPATHY AND CLINICAL PICTURES

| | Classical Exophthalmos | Paradoxic Exophthalmos |
|---|---|---|
| Lid retraction | Present | Absent |
| Proptosis | Slight or absent | Marked |
| Edema | Absent | Present |
| Ophthalmoplegia | Absent | Present |

It has been very difficult for us to classify our patients in one of the two groups, due to the overlapping of signs and symptoms of both clinical pictures. Nevertheless, if we try to separate the 50 cases into two categories —the retractopalpebral and the edematous-ophthalmoplegic—we would be obliged to include the ophthalmopathies of grade 1 in the first category, and the grades 2, 3 and 4 in the second.

Calculating the average of age and sex in both categories defined, we obtain the following results: in 13 cases of retractopalpebral exophthalmos, 12 women and one man. In 37 cases of edematous-ophthalmoplegic exophthalmos, 23 women and 14 men. The average age of the retractopalpebral type was 40 years, of the edematous-ophthalmoplegic type, 42 years.

As can be appreciated, we did not find the differences of age and sex observed by other authors. These and other observations make us believe, as Pochin and Rundle[10] do, that all aspects of endocrine ophthalmopathy vary only in degree, following a definite

cycle which depends on the activity of the pituitary gland and is more or less independent of the thyroid.

The conventional classification we conceived for practical purposes also presents difficulties in its application as the exophthalmos level is the most constant of all the signs and symptoms characteristic of each grade, and therefore it is the more useful for determining this grade, since the remaining signs and symptoms—including the orbital tension—are variable, to the point that the exophthalmos level of 25 or 30 mm. might be associated with a slightly increased or normal tension.

As to this, our findings contradict the ones obtained by Kearns, Henderson and Haines,[3] who state that the more the exophthalmos level rises in patients with Graves' disease, the higher is the degree of the orbital tension, there being a constant proportion between the one and the other. This discrepancy derives probably from the fact that these authors base their report on orbitonometric readings at a single point of progress of the ophthalmopathies they present, while we support our study with orbitonometric control, repeated every week or fortnight during a long period of time, from three months up to five years. On the other hand, our study enables us to confirm the observation made by Foster Moore[11] 20 years ago that the exophthalmos generally reaches its maximum at about three months, will remain unchanged for a time thereafter, will lessen gradually, with or without treatment, but will reach complete recovery only rarely.

Another interesting poir is the relation existing between the degree of thyrotoxicosis and ophthalmopathy. The degrees of thyrotoxicosis and ophthalmopathy are distributed as shown in the diagram of Figure 1. A graph of the relationship between the average degree of ophthalmopathy and the various grades of thyrotoxicosis renders this relation more evident (fig. 4). The curve obtained seems to indicate that the more pronounced ophthalmopathies are more frequently associated with high thyrotoxicosis than with euthyroidism, and that, on the contrary, the more moderate ophthalmopathies are associated with a greater frequency of slight thyrotoxicosis than pronounced hyperthyroidism; slight hyperthyroidism is characteristic of the edematous ophthalmoplegic exophthalmos.

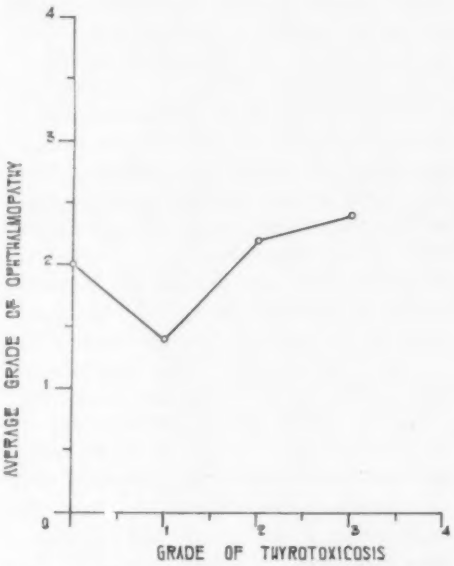



Fig. 4 (Gómez, Ferrer and Reforzo). Relationship between average grade of ophthalmopathy and various grades of thyrotoxicosis.

We shall now try to analyze the results obtained with the different treatments:

1. *Antithyroid drugs.* In seven of 28 patients these drugs produced a slight aggravation of the ophthalmopathy and in the 21 there was no appreciable change, which seems to indicate that the medical remission of the hyperthyroidism does not usually precipitate the malignant evolution of ophthalmopathy, which follows an independent course of the former, as it is affirmed by Dobyns.[12]

2. *Lugol.* In seven of the nine patients so treated, there was no change in the ophthalmopathy; in two we observed a slight aggravation. It may be stated that the iodine

therapy does not exert any influence whatsoever upon the ocular condition.

3. *Thyroidectomy.* We have performed for a long period of time, pre- and postoperatively, an orbitonometric follow-up study of seven patients with Graves' ophthalmopathic syndrome. Of these, four did not show any change in their ophthalmopathy, one had marked aggravation, one a slight impairment, and one improved slightly. This seems to indicate that, in a great majority of cases, the thyroidectomy does not have any influence, and in a minority it seems to be really harmful. The remaining cases in which the progress was doubtful are not considered. Naturally, the question could be raised as to the influence of thyroidectomy on the malignant evolution of the ophthalmopathy, since we cannot ascertain the outcome of the ophthalmopathy if the patient had not undergone surgery.

4. *Thyroid.* We administered thyroid to 28 patients with ophthalmopathies, the majority of second and third grades. Eleven of these patients did not demonstrate signs of thyrotoxicosis and had a normal basal metabolism rate; two presented a third-grade thyrotoxicosis; 13 suffered from a second-grade thyrotoxicosis; the remaining two had the first grade. Seven of the 11 euthyroid patients did not develop changes in their ocular condition, two showed a slight aggravation and two a slight improvement. Of the two patients with third-grade thyrotoxicosis, one responded with marked aggravation and the other had an indifferent result. In 11 of the 13 cases with second-grade thyrotoxicosis, the thyroid powder was ineffective; in one case it was decidedly harmful; in the last case it was slightly favorable. Of the two cases with first-grade thyrotoxicosis, the therapy was clearly beneficial in one case and had no effect in the other. As has been demonstrated, of 28 ophthalmopathies treated, 20 did not react at all to the treatment, and only one experienced a remarkable improvement.

5. *Acetazolamide.* The drug was administered to 99 patients all of whom suffered from ophthalmopathy of second, third of fourth grades with somewhat pronounced signs of palpebral and orbital edema. In five of nine cases the edema decreased slightly or markedly, but the improvement was generally temporary. It is noteworthy that we could prove in two cases a decisive improvement of palpebral retraction, which speaks in favor of the theory that, in a few cases, palpebral retraction is to be attributed to the immobility of the elevator muscle resulting from edematous infiltration.

The exophthalmos level and the degree of orbital tension, orbitonometrically measured, did not change in eight of the nine cases; in the remaining case they increased, indicating an aggravation of the condition. We were not able to determine its relation to treatment.

6. *Corticotropin and cortisone.* In nine cases treated with ACTH and examined orbitonometrically before, during, and after treatment, we could not observe any change in the level and tension of the ophthalmopathy. These results are similar to those obtained by Brain,[13] who presents 28 cases of endocrine exophthalmos treated with ACTH or cortisone of which only three improved.

7. *Hyaluronidase.* We tried this enzyme in four patients by retrobulbar injection. In each case we performed three orbitonometric measurements: the first, immediately before the injection, the second 10 minutes after the injection was given, and the third one hour later. This procedure permitted confirmation in two cases of an immediate, slight and temporary elevation of the orbital tension, which returned to its normal within an hour. In the two remaining cases, no immediate or late changes were observed. The temporary increase of the tension should be considered physiologic, due to the fluid introduced and which is absorbed more or less quickly, depending on individual circulation.

8. *Other steroids and hormones.* We have tried administration of testosterone with completely negative results in two male patients of about 50 years of age. In two in-

stances we applied retrobulbar cortisone injections, with detrimental results, since we obtained a slight temporary aggravation in one case and a pronounced temporary one in the other of all symptoms and particularly of the edema.

9. *Radiotherapy of the orbit.* We have treated six cases of progressive ophthalmopathies with radiotherapy of the orbit. In four of them the results were nonsignificative with regard to the level and tension but the inflammation and the edema improved slightly. These four ophthalmopathies showed a subacute or slow evolution and the radiotherapy was applied during a quiescent period. The orbitonometric and inflammatory condition of one of the two remaining cases improved slightly; in the other a slight aggravation of all the symptoms took place. The first of these cases was an exophthalmos of acute development treated during the quiescent period, and the second, also an exophthalmos of acute development, was treated during the period of acute attack. The ophthalmopathy presented similar orbitonometric oscillations in both cases for a long time after discontinuing the treatment, that is, the first case remained stationary and the second gradually became worse.

10. *Radiotherapy of the pituitary gland.* We have been treating four patients with pituitary radiotherapy at high dosage levels. In all of them the treatment was started more than a year after the onset of the ophthalmopathy, which permits its classification as late and which renders improbable the benefits of this therapy, according to Beierwaltes.[14] Three of the four patients presented a fourth grade exophthalmos at the time of radiotheraphy and no positive results were achieved. The first of these three presented a slight syndrome of hyperthyroidism which was aggravated following the treatment; the second, a patient with normal thyroid function, also developed a thyrotoxic crisis after treatment, with an increased basal metabolism rate, swift and pronounced loss of weight, tachycardia, nervousness, and so forth; the third, who had been thyroidectomized and presented a basal metabolic rate below the normal level, was the only one of the three who did not show subsequent symptoms of active hyperthyroidism. Only the fourth patient who had a third-grade ophthalmopathy, evolving more slowly and more benignly than the other three, was benefited by the pituitary radiotherapy. This last patient showed slight symptoms of thyrotoxicosis which did not seem to be aggravated as a consequence of treatment.

## Conclusions

1. Of the total 50 cases of Graves' ophthalmopathy, females represented 70 percent.

2. We have not observed difference in age and sex in mild, moderate, or pronounced exophthalmos.

3. Mild and moderate cases are more often accompanied by a slight grade of hyperthyroidism and less frequently by pronounced thyrotoxicosis. Pronounced cases are usually accompanied by a marked thyrotoxicosis and less frequently by euthyroidism. These observations contradict some widely accepted premises.

4. We do not find any difference in age and sex or characteristics of thyroid function, emphasized by other authors, to justify the division of the ophthalmopathies in two groups—retractopalpebral and the edematous ophthalmoplegic.

5. The level of exophthalmos is the most constant ocular sign and every classification should be based primarily on it. In any case, the classification is conventional, as is the one we present. Our experience seems to point out that all the aspects of the ophthalmopathy represent periods of a cycle that depends especially on pituitary activity.

6. In general, the treatments we have tried do not seem to be effective in reducing the exophthalmos level or the grade of the orbital tension; therefore, we are pessimistic with regard to the therapeutic measures at our disposal.

7. The antithyroid drugs will not improve the ophthalmopathy but they should always be used when there exists an active hyperthyroidism, without fearing too much the aggravation of the ocular condition. Nevertheless, it might be dangerous to try to normalize the basal metabolic rate of the patient, since the resulting hypothyroidism might aggravate the edema of the orbit by retention of water in the tissues.

8. There are no objections to performing a thyroidectomy when goiter and thyrotoxicosis justify it, since the surgical remission of hyperthyroidism—as well as the medical one—does not precipitate the malignant phase of the ophthalmopathy, which follows an independent course.

9. Acetazolamide and radiotherapy of the orbit may be useful only in reducing the edema and congestion of the lids and conjunctivas if a justifiable degree of these symptoms exists.

10. Perhaps the radiotherapy of the pituitary may be useful, provided it is employed early and only in cases without active hyperthyroidism. At any rate, we favor thyrostatic treatment in all the cases where the thyroid gland has not been removed.

11. The parenteral administration of corticotropin and the retrobulbar injection of hyaluronidase are of no benefit.


## Summary

Fifty patients with Graves' disease have been studied. A classification according to the intensity of the thyrotoxicosis and another according to the degree of the ophthalmopathy are proposed. A diagram showing the distribution of the different grades of thyrotoxicosis and ophthalmopathy is presented, and the characteristics of the curve thus obtained are emphasized. The evolution of the ophthalmopathy is analyzed, and the results of the different treatments in the light of repeated orbitonometric examinations are discussed.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*Rivadavia 1993.*

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# HEALING PROCESS IN THE MECHANICAL DENUDATION OF THE CORNEAL ENDOTHELIUM*

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The endothelium plays an important role in the transparency of the cornea. Damage to it causes the cornea to imbibe excessive fluid from the aqueous, with resultant edema and loss of transparency. Leber (1873)[1] was the first to demonstrate the importance of the endothelium in corneal transparency. More recently Cogan (1949)[2] reported a study of regeneration of corneal endothelium based on biomicroscopic examination of experimental animals. He observed cloudiness of the cornea due to injury to the endothelium and found that healing was rapid and complete in the presence of a normal Descemet's membrane.

Although the histologic study of regeneration of the corneal endothelium has been reported by Nagano,[3] Fuks,[4] Stocker,[5] and Binder and Binder,[6] the healing process in the regeneration of the corneal endothelium remains as yet incompletely understood. All these reports on the regeneration of the corneal endothelium after trauma, however valuable, were based on injuries that were not quite standardized and a clear appreciation of the morphologic changes of the regenerating endothelial cells was lacking. Detailed observation of the pattern of regeneration and the fate of the individual cell at the margin of the defect appeared desirable. We believed that further histologic studies combining the flat-preparation and phase-contrast microscopy might contribute to a better understanding of the extremely interesting healing process taking place after mechanical injury of the corneal endothelium.

* From the laboratory of The Eye-Bank for Sight Restoration, Inc., Manhattan Eye, Ear and Throat Hospital. This study was supported by Research Grant B 1130 (C2) from the National Institutes of Health, Public Health Service.

## Materials and Methods

The present study was conducted on young chinchilla rabbits, 1.8 to 2.3 kg. in weight. The rabbits were anesthetized with intravenous sodium nembutal. A keratome incision was made through the sclera about one mm. from the limbus at the 12-o'clock region. Two types of mechanical denudation of the corneal endothelium without involving the Descemet's membrane were performed on 82 rabbit eyes under sterile precautions. Minute injuries were made on 24 eyes by pricking the endothelium with a blunt 27-gauge needle. Large wounds in the shape of vertical bands were produced in 58 eyes by denudation of about one fourth of the corneal endothelium with a blunt spatula. Great care was taken to create standard wounds by using a blunt spatula inserted into the anterior chamber up to a mark 12 mm. from its tip. The spatula was bent at an angle so that it could be applied to the endothelial surface of the cornea from limbus to limbus. Control of the extent of denudation was finally achieved with increased practice and standardization of the method.

Immediately after injury the denuded area of endothelium thus obtained measured 7.6 to 8.0 mm. in length and 2.3 to 2.5 mm. in width (approximately one fourth of the corneal endothelium) in eight rabbit eyes. Our initial attempts at minute injuries of the corneal endothelium with a small sharp needle, as described by Stocker,[5] were unsatisfactory from the technical standpoint and were excluded from this series.

The eyes were examined with the slitlamp biomicroscope at varying intervals for clinical observation. After periods of from five hours to eight weeks, the animals were anesthetized and the corneas removed. The

animals were then killed with intravenous injection of air. A one to two mm. tag of sclera was left at the 12-o'clock region of the excised cornea for convenience in handling, since the application of any instrument to the corneal endothelium was to be avoided.

In this study the corneas were fixed in one of three ways:

1. The fixative, either 10-percent neutral formol-saline or 1.0-percent buffered osmic acid (pH 7.4-7.8), was injected into the anterior chamber with a 27-gauge needle. Immediately after this injection the cornea was removed and placed in a large volume of the same fixative.

2. The corneas were excised from anesthetized rabbits and immediately placed in 10-percent neutral formol-saline.

3. In some cases the removed corneas were fixed after supravital staining with silver nitrate or alizarin red to demonstrate the intercellular cement substance of the endothelium.

In a few cases the whole intact eye was immediately fixed in formol-saline. This method was excluded from this investigation because the endothelium developed postmortem changes.

The flat preparations, involving the endothelium, Descemet's membrane, and as little as possible of the stroma were stained with hematoxylin only and mounted with the endothelial surface up to study the endothelium with phase-contrast and ordinary light microscope. The rest of the cornea was embedded in paraffin and sectioned for histologic study, staining with hematoxylin and eosin, toluidine blue, periodic acid-Schiff and van Gieson stains.

## Observations and Results

### I. Study of flat preparations

*Normal corneal endothelium of rabbits.* Eight normal rabbit eyes were examined for comparison. The normal endothelial cells were mostly hexagonal in shape and of uniform size with kidney-shaped nuclei containing no perceptible nucleoli under either phase-contrast or ordinary light microscope (fig. 1-A and B). Amitotic cell division was found in normal endothelium, but no mitosis could be seen (fig. 1-B).

*The healing process.* After mechanical

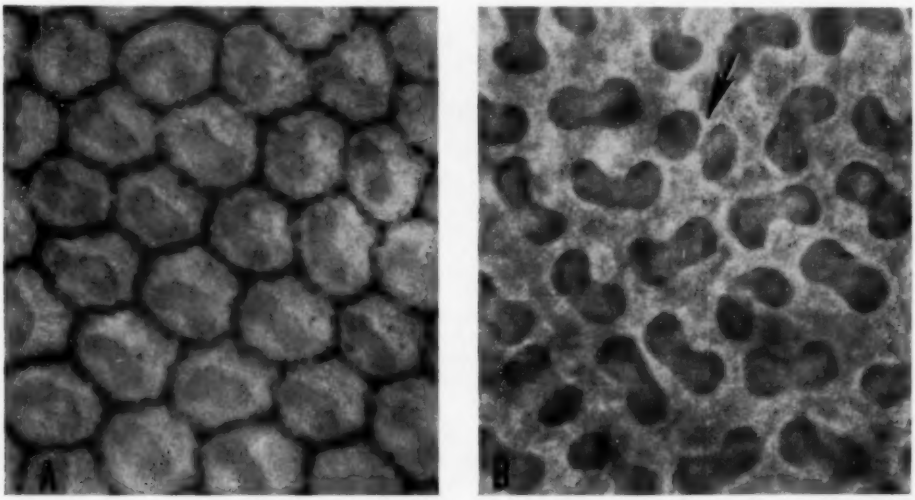

Fig. 1 (Chi, Teng and Katzin). Normal rabbit endothelium. (A) The cells are mostly hexagonal in shape and of uniform size. (147 O.S., alizarin red stain, flat preparation, ×800.) (B) Normal kidney-shaped nuclei, evenly distributed; arrow indicates amitotic cell division. (846 O.D., hematoxylin, phase contrast, flat preparation, ×800.)

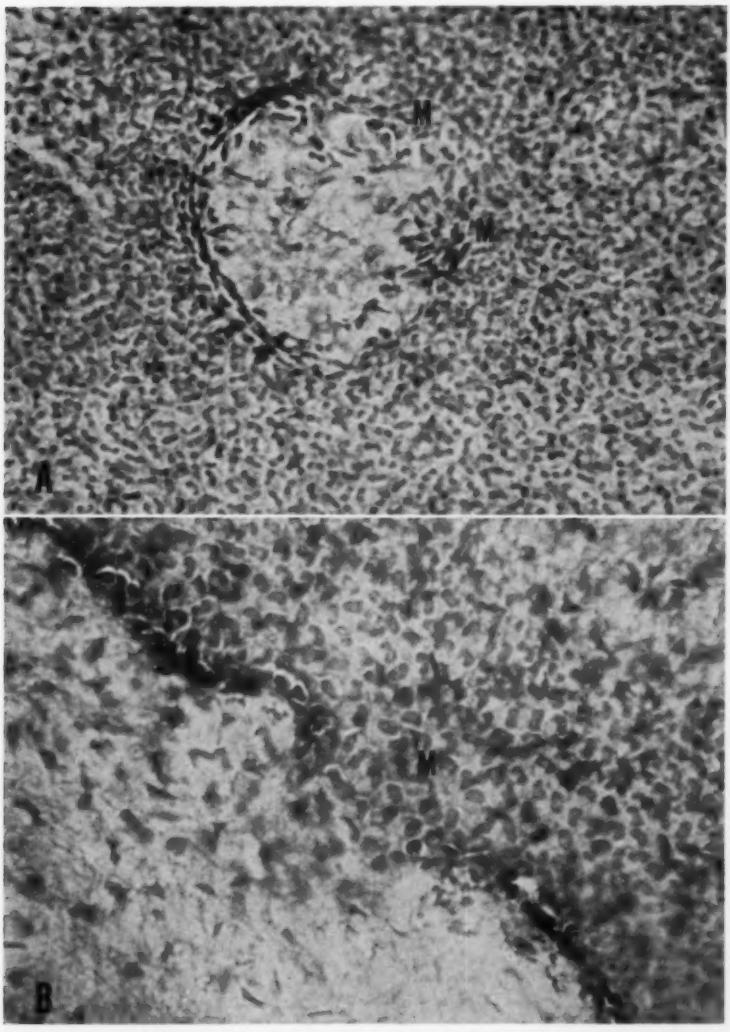


Fig. 2 (Chi, Teng and Katzin). Mechanical injury of the corneal endothelium showing a sharply outlined defect bordered by pyknotic injured cells which are compressed with their long axis tangential to the defect. In spot (M) the cells have begun activation and migration. (Hematoxylin, phase contrast, flat preparation.) (A) Five hours after minute injury (866 O.D., ×200). (B) Twelve hours after large injury (90 O.D., ×220).

denudation the corneal endothelium healed in the following manner:

1. Activation and migration. We first observed activation and migration of the marginal cells of the wound. Five hours after the injury there was a sharply outlined defect bordered by pyknotic injured cells which were compressed with their long axis tangential to the defect (fig. 2-A). In a few spots the cells along the margin of the denuded area had become larger and were of various sizes and shapes; some were elongated and arranged radially, showing many pseudopodial processes extending

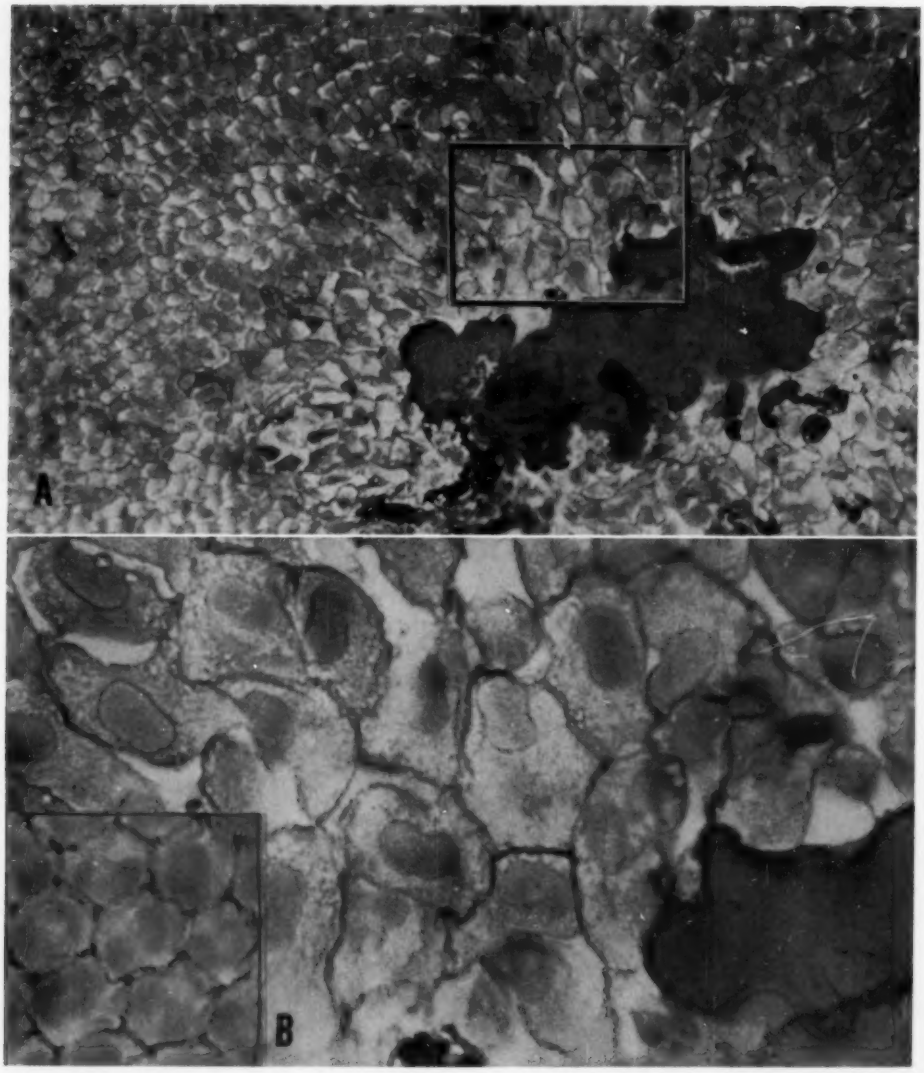


Fig. 3 (Chi, Teng and Katzin). (A) 17 hours after minute injury. The marginal cells have become larger and are of various sizes and shapes. They are migrating radially toward the defect. (820 O.S., supravital silver nitrate stain, flat preparation, ×220.) (B) High-power view of the marked area of Fig. 3A. Compare with inset of the normal endothelial cells in the same magnification (×800).

toward the area of the defect (figs. 2-A and B, 3-A and B, 4 and 5). Their nuclei appeared to be enlarged and showed a great increase in visible chromatin which was aggregated either in irregular masses or in a single nucleoluslike form (figs. 4 and 5). The kidney-shaped nuclei gradually changed into an oval shape (figs. 4 and 5). Migration of the activated cells was pronounced 20 to 22 hours after injury.

2. CELL DIVISION. Both amitosis and mitosis were present. Amitosis appeared early.

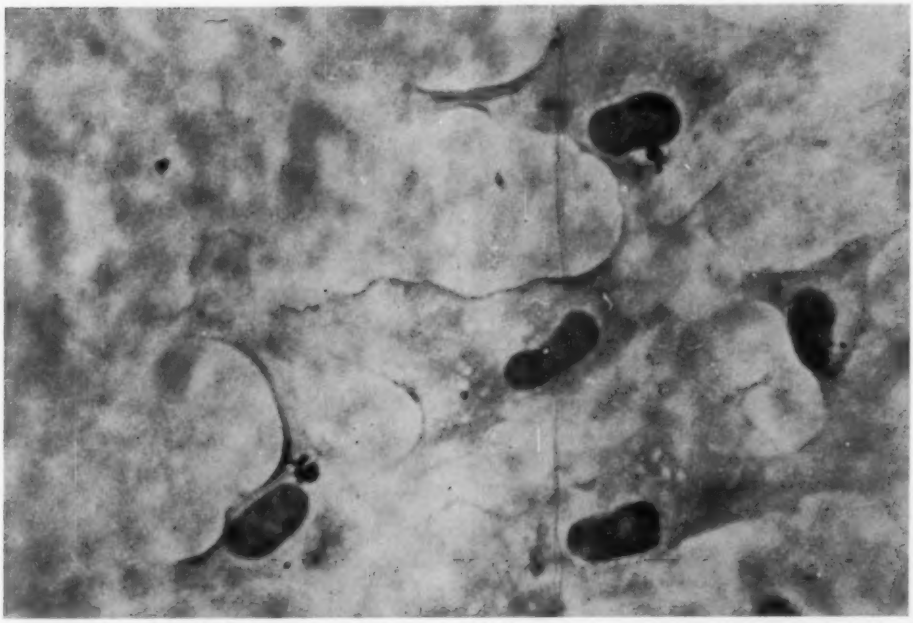

Fig. 4 (Chi, Teng and Katzin). Twenty-four hours after injury. The marginal cells are much enlarged with many pseudopodial extensions directed toward the denuded area. Compare with Figure 1 showing normal endothelium in the same magnification. (75 O.D., hematoxylin, phase contrast, flat preparation, ×800.)

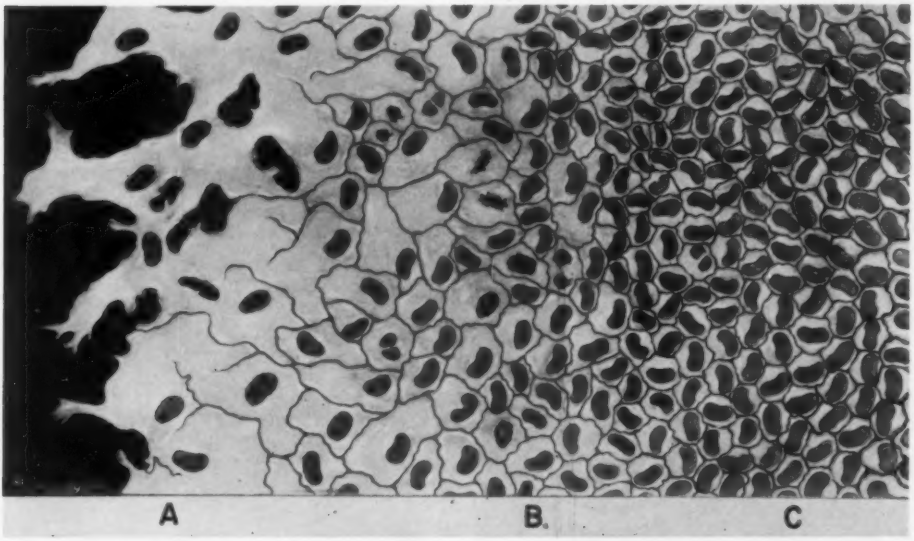


Fig. 5 (Chi, Teng and Katzin). This composite drawing shows the healing of a large mechanical denudation of the corneal endothelium 24 to 48 hours after injury. The marginal cells are migrating over the site of the injury and the cells in the zone further back are undergoing mitosis. (A) Zone of activated marginal cells. (B) Zone of cell division. (C) Zone of normal unchanged endothelial cells.

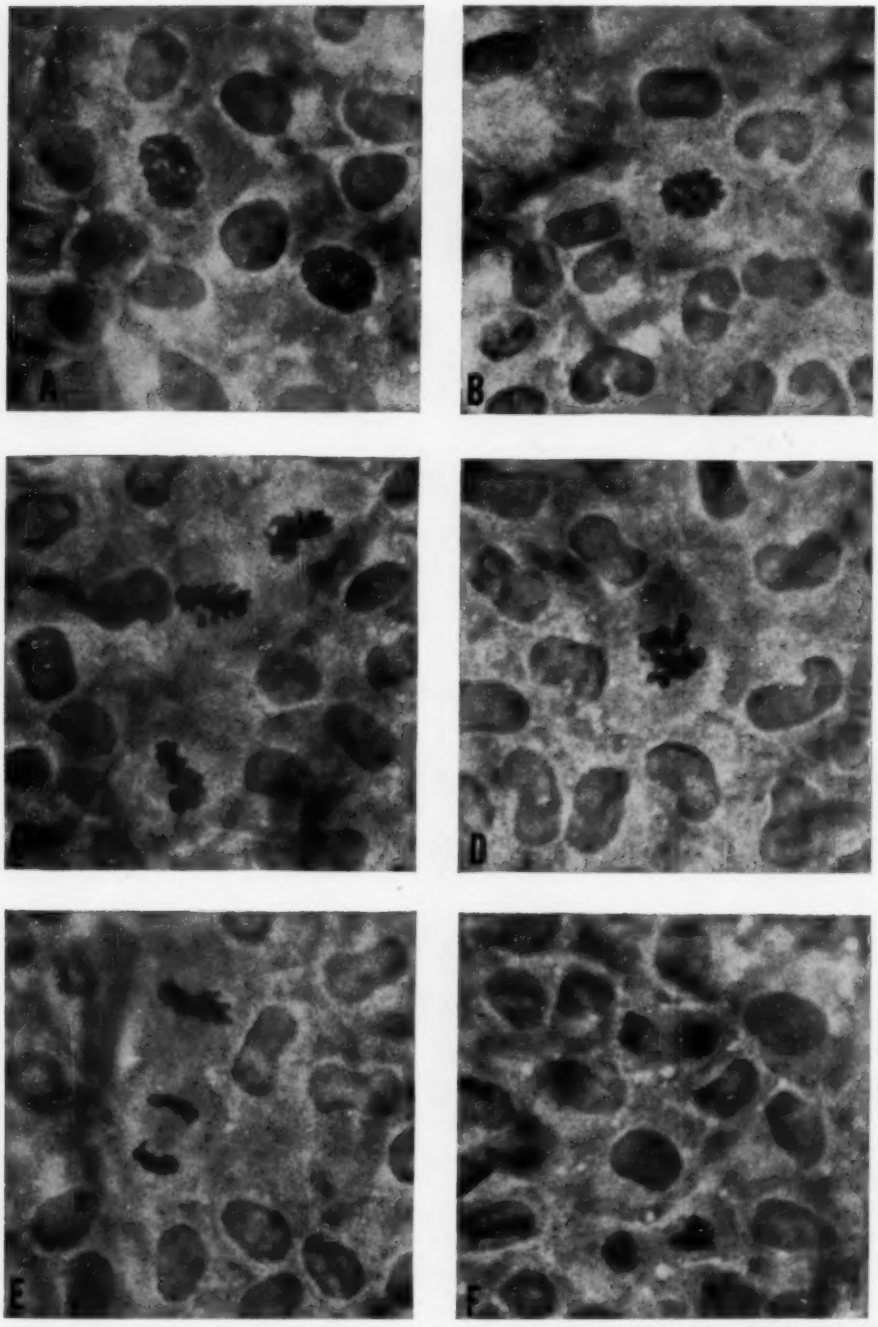


Fig. 6 (Chi, Teng and Katzin). Showing various stages of mitosis (hematoxylin, phase contrast, flat preparation, ×800). (A, D and E) 49 hours after injury (852 O.D.). (B, C and F) 45 hours after injury (854 O.S.).

Five and seven hours after injury, amitosis increased (three to five cells in one 8.0 by 40 field in some areas) at the periphery of the zone of activated and migrating cells. No mitotic cell division was found 20 to 22 hours after injury; most often mitosis began 24 hours after denudation. Most of the mitotic cells were observed at some distance from the denuded area (fig. 5); occasionally one could be found among the cells which had migrated to the margin of the wound and a few occurred among the cells spreading over the defect. Cell division by mitosis increased to a peak in 48 to 55 hours and then gradually decreased. Mitotic figures in all phases could be observed (fig. 6). In large wounds (about one fourth of the endothelium) mitotic figures had practically disappeared from the denuded area after 96 hours, but amitosis still took place at a more than normal rate after seven weeks. No cell division took place in minute wounds.

3. Restoration. After 17 hours a minute injury (0.210 by 0.133 mm.) was completely covered by migrating cells without any cell division (fig. 7-A). Large wounds were completely covered 72 hours after injury. The newly covered areas could be recognized by the irregular distribution of cells of various sizes and shapes (fig. 7-A and B.) Their nuclei contained nucleoli or collections of chromatin. There were a number of large cells with very large nuclei (fig. 8). In the course of the succeeding weeks the newly formed endothelial cells underwent many changes and were gradually rearranged and transformed into a normal appearance and pattern. Four weeks after injury most of the cells appeared normal in size and shape. Only a few abnormally large cells remained, surrounded by normal cells in rosette form (fig. 9). Eight weeks after injury the endothelium had completely regained its normal appearance.

## II. Slitlamp biomicroscopic observations and histologic findings

One-half hour after injury the corneal stroma over the area of damaged endothelium began to swell and turn opaque, a process which spread rapidly so that the stroma reached a maximum turbidity in four hours. This edematous appearance of the cornea remained unchanged for a day or two after which the opacity cleared, leaving no residual cloudiness four or five days after injury. As the endothelium completely covered the denuded area (average, 72

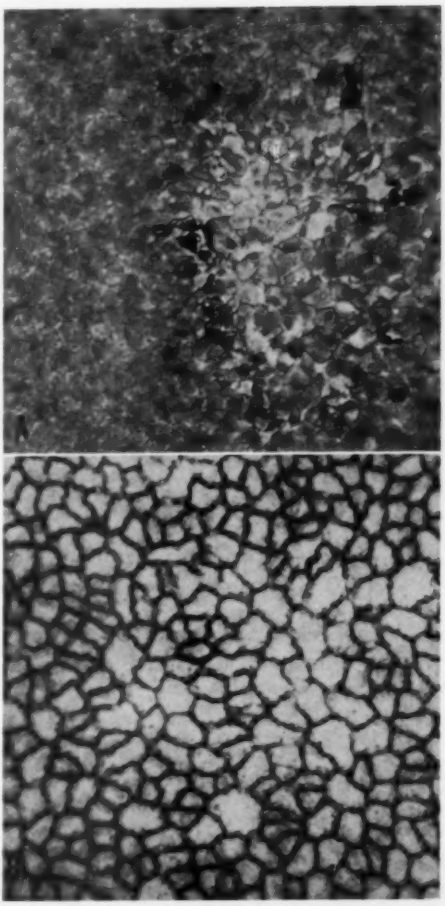

Fig. 7 (Chi, Teng and Katzin). The denuded area is completely covered by irregularly distributed cells of various sizes and shapes (flat preparation). (A) A minute injury is completely covered by migrating cells 17 hours after injury (82 O.S., supravital silver nitrate stain, ×220). (B) A large wound is completely covered by migration and mitosis 72 hours after injury (147 O.D., alizarin red, ×220).

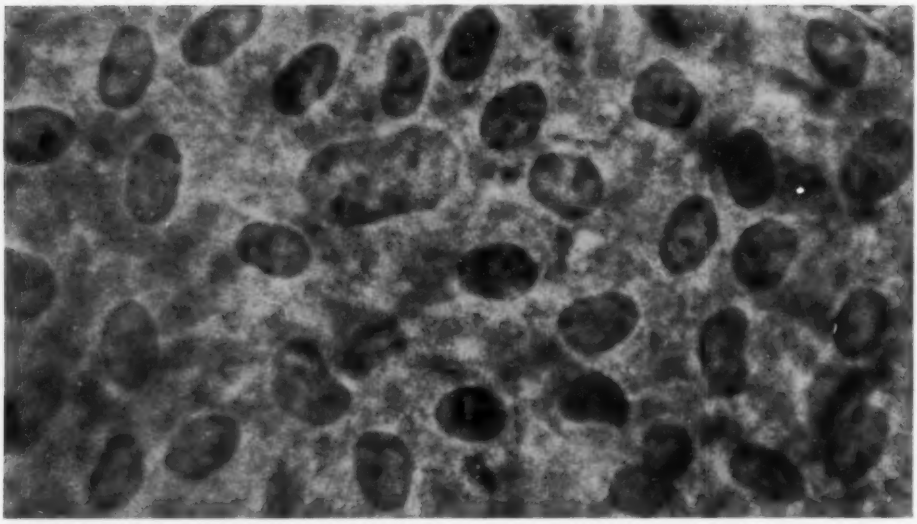

Fig. 8 (Chi, Teng and Katzin). Ninety-six hours after injury. The nuclei of the newly formed cells are variable in size and shape and contain aggregated chromatin or nucleoli. One cell has a very large nucleus (71 O.S., hematoxylin, phase contrast, flat preparation, ×800).

hours), the edema of the stroma subsided gradually, usually one or two days after the cell covering was complete.

In the minute injuries the only noticeable change was the appearance of tiny white spots immediately adjacent to the injured endothelium.

Histologic sections of the large wounds showed marked edema of the stroma from four hours to one or two days after injury, the edema gradually decreasing at a rate corresponding to the slitlamp biomicroscopic findings. The edematous stroma revealed less metachromasia in toluidine blue

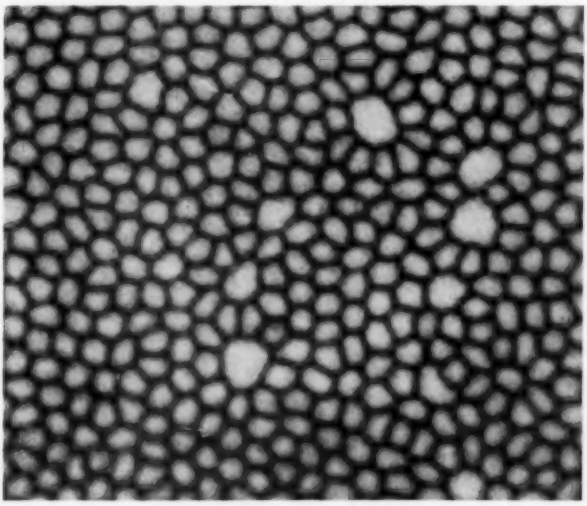

Fig. 9 (Chi, Teng and Katzin). Four weeks after injury some of the large cells are surrounded by cells of normal size forming a rosette and arranging themselves in an almost normal regular pattern. Compare with Figures 1, 7, and 8. (129 O.D., alizarin red, flat preparation, ×220.)

than is normal. There was no inflammatory cell infiltration of the stroma noted at any time.

## Comment

Our observations of normal rabbit corneas confirmed the findings of previous investigators that mitoses are never seen in normal endothelium[2, 6] and under normal conditions the regeneration of the corneal endothelium occurs by amitosis.[6]

We had the same experience as Speakman[7] who mentioned in his article that fixing the excised corneas of anesthetized rabbits with formalin is better than fixing the whole intact eye. But we found that injection of neutral formol-saline or buffered osmic acid into the anterior chamber of the anesthetized rabbits was the best method of all. In this last method there were no fine vacuoles of the cytoplasm of the endothelial cells, usually the first sign of post-mortem change. Osmic acid-fixed tissues, however, take ordinary stains poorly, and our best results were obtained by injection of formol-saline. In the supravital staining with alizarin red or silver nitrate, we were fully aware that there were changes, but it still served our purpose of observation of the pattern of the endothelium very well.

A few of our initial attempts at minute injuries of the corneal endothelium with a small sharp needle as described by Stocker[5] were excluded from this study because the wound always involved the Descemet's membrane. The edges of the perforations in Descemet's membrane were seen in phase-contrast microscopy (figs. 10 and 11) and could be confirmed by serial sections of the flat preparations. There were accumulations of regenerated cells along the edges of the punctures (figs. 10 and 11). When the injuries involve Descemet's membrane, the stromal cells participate in the healing process and the defects appear to be covered by an irregular mass of cells most of which have elongated nuclei. Wounds in which Descemet's membrane was ruptured take a much longer time (48 to 68 hours) to cover the injured area completely, than do the minute injuries produced by a blunt needle and not involving Descemet's.

Clinical examination 24 hours after injury showed the anterior chamber to be filled with secondary aqueous containing fibrin which occasionally adheres to spots at the edge of the denuded area of the endothelium. Flat preparations showed that fibrin strands had enmeshed some polymorphonuclear leukocytes at the adherent spot.

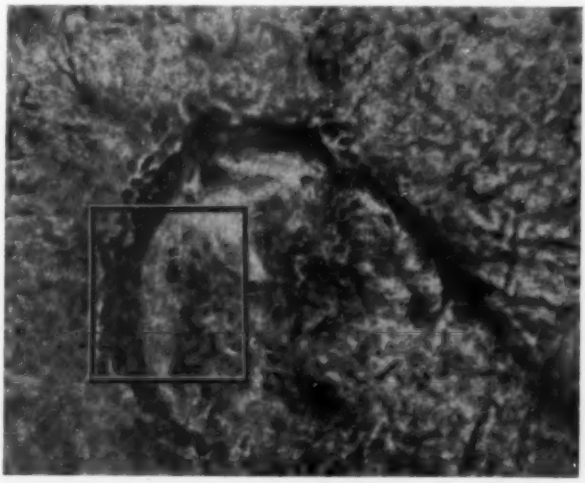

Fig. 10 (Chi, Teng and Katzin). Minute injury with rupture of Descemet's membrane showing the accumulation of regenerated cells along the edges of the puncture. Fifty-three hours after injury the minute defect is not yet completely covered by endothelium. (9 O.S., hematoxylin, phase contrast, flat preparation, ×220.)

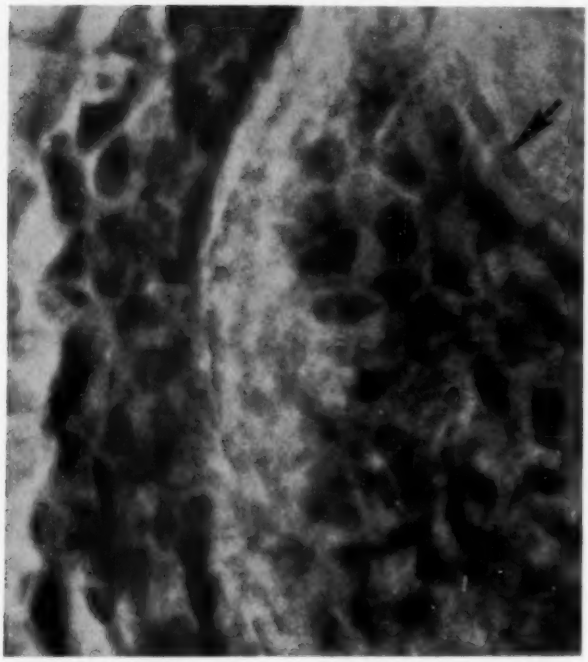

Fig. 11 (Chi, Teng and Katzin). High-power of marked area of Figure 10. Arrow indicates the edge of the ruptured Descemet's membrane (×800).

These cells, found in three out of the 58 large wounds, were the only inflammatory cells found throughout the whole process of regeneration. We found no lymphocytes such as Binder and Binder described in their paper.[6]

In reviewing the literature only Nagano[3] and Binder and Binder[6] mentioned the cells with very large nuclei. Nagano gave no interpretation of the nature of these cells, but Binder and Binder thought that these large cells might be macrophages originating from the endothelium by metaplasia.

In the very beginning of the regenerative process cell migration and division start at different spots in every direction from the margin of the denuded area and work toward the wound with the result that cells of variable size and shape form an uneven cover for the wound. In the course of the succeeding weeks the regenerating cells undergo many changes and are gradually rearranged and transformed into a normal appearance and pattern. The large cells are probably a transitional state of the regenerating cells; in Figure 9, for instance, taken four weeks after injury, some of the large cells are surrounded by cells of normal appearance forming a rosette and arranging themselves in an almost normal, regular pattern.

Fuchs[8] and Stocker[5] expressed doubt as to whether a regular endothelial cover could ever be regenerated after the endothelial cells have been destroyed. The regenerated layer, they believed, would be more similar to connective tissue than to the original cells. This may hold true for perforating injuries in which there is a reaction of the underlying tissues. But if the damage is confined to the endothelium only, the regenerated endothelium does regain its original normal pattern, although it takes a relatively long time. When about one fourth of the endothelium is denuded, Descemet's membrane is covered by a newly formed endothelium in an aver-

age of 72 hours. The edema of the cornea then disappears one or two days later, even though the regenerated cells are not yet normal in appearance. This stage is attained at the end of eight weeks.

## Summary and Conclusions

The healing process in mechanical denudation of the corneal endothelium in rabbits is accomplished by cell activation, migration and multiplication. Migration of the activated cells from the margin of the denuded area occurs first and is followed by amitosis and mitosis beginning at some distance from the defect and playing a secondary role.

The activation and migration of the marginal cells is shown in their enlargement and the throwing out of active pseudopodial extensions into the denuded area. Their nuclei become oval shaped and contain collections of chromatin sometimes resembling nucleoli. Minute injuries are completely covered by cell activation and migration without initiating mitotic activity.

A denudation of about one fourth of the corneal endothelium is completely covered 72 hours after injury. Thus a fairly large area of endothelial injury is completely covered in a comparatively short time. The edema of the cornea then disappears one or two days later even though the regenerated cells are not yet normal in appearance. The newly formed endothelium undergoes many changes through transformation and rearrangement, regaining its normal appearance and pattern after eight weeks.

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# RESULTS OF IMPLANTATION OF INTRAOCULAR LENSES IN UNILATERAL APHAKIA*

### With special reference to the pupillary or iris clip lens—a new method of fixation

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## A. Ridley's method (fixation of the lens prothesis in the so-called natural position)

At the meeting of the Dutch Ophthalmological Society on May 12, 1956, at Groningen, Holland, the results obtained with Ridley's method in 12 patients with unilateral or predominantly unilateral cataract were presented. At that time the patients had been observed for five to eight months. In December, 1958, 11 of these patients were again examined (one patient had died in the meantime). The length of observation had then been 36 to 39 months. The favorable appear-

* From the Department of Ophthalmology, St. Elisabeth Hospital, Sluiskil, Holland. Read before the Dutch Ophthalmological Society, December, 1958, Leiden, Holland.

TABLE 1

VISUAL ACUITY OF EYES WITH RIDLEY LENS

| Patient No. | Visual Acuity after 5–8 Months | Visual Acuity after 36–39 Months | Conditions without Relation to Tolerance |
|---|---|---|---|
| 1 | 6/6 | 6/9 | |
| 2 | 2/60 | Deceased | Lesion of Descemet's membrane during operation |
| 3 | 6/9 | 6/12 | |
| 4 | 6/12 | 6/9 | |
| 5 | 6/9 | 6/12 | |
| 6 | 6/12 | 6/4.5 | |
| 7 | 6/9 | 6/9 | |
| 8 | 6/4.5 | 6/4.5 | |
| 9 | 5/15 | 5/15 | Retinal degeneration |
| 10 | 6/18 | 6/9 | |
| 11 | 6/12 | 6/6 | |
| 12 | 6/24 | 6/36 | Amblyopia |

ance of the operated eyes had been fully maintained: there had been no luxations of intraocular lenses, the media were as clear as before, the intraocular pressures were within normal limits, and there were no inflammatory or degenerative changes. In a few instances there even was an improvement of the visual acuity from May, 1956, to December, 1958 (table 1).

Although Ridley's procedure is too precarious for general application, it does appear that after a carefully performed operation the Ridley prothesis is very well tolerated, even for longer periods of time. It should be particularly noted that the contact of the lens with the posterior surface of the iris does not give rise to any complications, which is of importance in view of the further development of the intraocular lenses.

B. THE METHODS OF STRAMPELLI, DANNHEIM AND OTHERS (fixation of the lens prothesis in the anterior chamber angle)

A total of 44 implantations of intraocular lenses with supports in the anterior chamber angle were performed. Of these lenses, 35 were of the so-called rigid type (Strampelli, et al.) and nine of the elastic type (Dannheim). Insertion into the anterior chamber is much easier than Ridley's operation and can be done as a deferred procedure. Moreover, it has the advantages of a wider range of indications, adaptation to individual specifications, and impossibility of luxation.

Reviewing the results of the 35 implantations of anterior chamber lenses with rigid supports in the chamber angle (table 2), it appears that the visual acuity after six months is in general very good. Of the 29 aphakic eyes, that had some form of acquired cataract, 26 have a visual acuity of 6/12 or better. The prothesis is very well tolerated (fig. 1). The eyes with aphakia after congenital cataract have been excluded from this table, as the determination of the visual acuity was very difficult. In these latter cases, too, the organic optic result was very good.

A review of the same group of eyes one year after the implantation yields less favorable results, however. During the second six-month period, the cornea had developed some cloudiness in several cases. In one case the lens was removed but without any subsequent improvement of the corneal condition. After the first year practically no changes were observed. Another lens was removed, but again without any effect on the corneal cloudiness.

We observed cloudiness of the cornea, as a late complication after the implantation of anterior chamber lenses with rigid supports in the chamber angle, in nine out of 35 eyes. This cloudiness occurred in some cases only in a small peripheral area of the cornea, with

TABLE 2

VISUAL ACUITY OF EYES WITH RIGID ANTERIOR CHAMBER LENS
(29 patients with unilateral aphakia after acquired cataract)

| Visual Acuity | 6/60 or less | 6/36 | 6/24 | 6/18 | 6/12 | 6/9 | 6/6 | 6/4.5 |
|---|---|---|---|---|---|---|---|---|
| No. eyes | | | 6 mo. after insertion | | | | | |
| | | | 2 | 1 | 8 | 10 | 4 | 4 |
| No. eyes | | 1 yr. after insertion (1 lens prothesis removed) | | | | | | |
| | 4 | 2 | 3 | 3 | 3 | 5 | 4 | 4 |
| No. eyes | 18 mo. after insertion (2 lens protheses removed, 1 patient deceased) | | | | | | | |
| | 5 | 1 | 1 | 4 | 3 | 4 | 4 | 4 |

little or no interference with vision, but was more severe in other cases (fig. 2).

The corneal cloudiness, the cause of which is edema, did not respond to any treatment. Increase of intraocular pressure could definitely be ruled out. It is evident that the

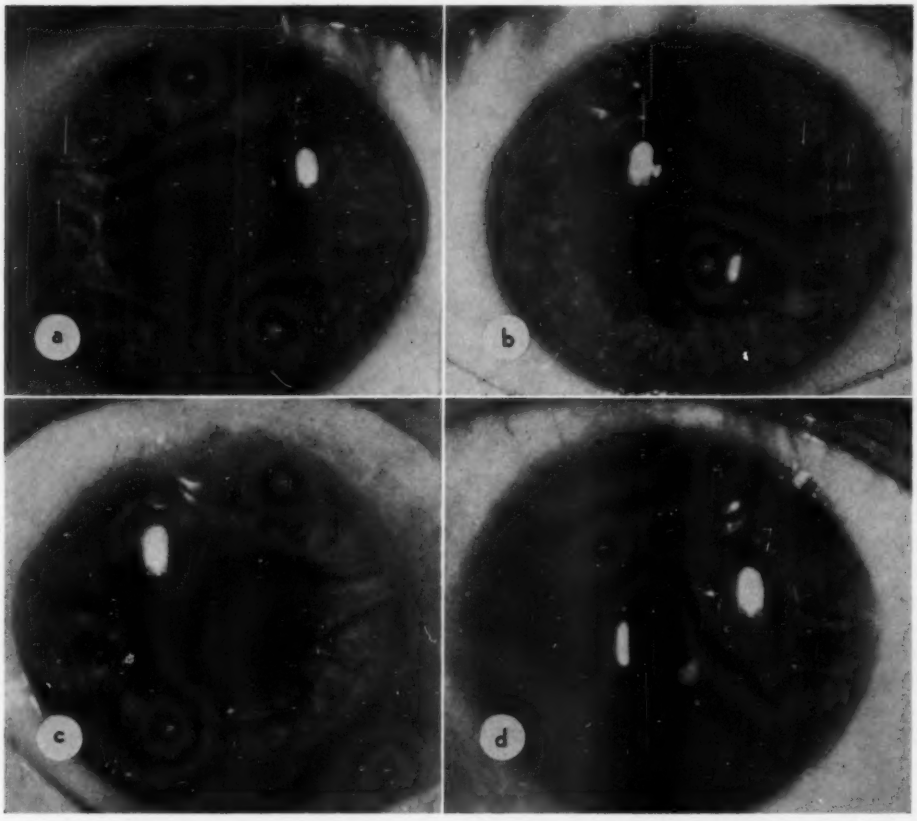


Fig. 1 (Binkhorst). Intraocular lenses in the anterior chamber, with rigid supports in the chamber angle. (a) In aphakia after unilateral congenital cataract. (b) In aphakia after unilateral traumatic cataract. (c) In aphakia after unilateral cataract of unknown etiology. (d) In aphakia after predominantly senile cataract.

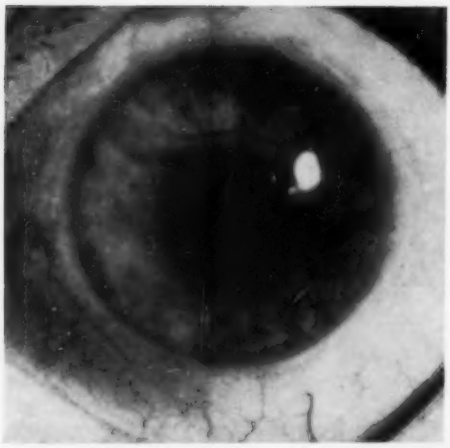

Fig. 2 (Binkhorst). Edema of the inferior half of the cornea. Onset nine months after the implantation of an intraocular lens in the anterior chamber, with rigid supports in the chamber angle.

cause of this late corneal edema is damage to the endothelium. The following observations suggest that this damage is brought about mechanically by the lens prothesis, rather than through a toxic inflammatory process:

1. Patients with a rigid anterior chamber lens usually complain about hyperesthesia of the eye to touch.

2. In some patients the corneal edema followed rubbing of the eye.

3. No further cases of corneal edema were observed after all patients had been explicitly warned against rubbing or even touching the eye.

4. Finally, we have been able to observe directly some actual lesions caused by these lens protheses. Two eyes were examined histologically, one post mortem, the other after enucleation on patient's request because of pain. In both instances there was a tissue defect in and around the anterior chamber angle, in one eye even extending into the ciliary muscle. There were no signs of inflammation (fig. 3).

Slitlamp examination revealed in four out of these nine patients with late corneal edema more centrally located lesions, consisting of linear scars in the posterior layers of the cornea, parallel to the inferior border of the intraocular lens. Apparently these lesions are due to contact of the intraocular lens with the cornea. In one patient we observed the onset of edema following such a lesion of the cornea (fig. 4).

The late occurrence of corneal edema after the implantation of anterior chamber lenses has been observed by other surgeons too.

It seems important, therefore, to strive for the prevention of these lesions in the anterior chamber. Already more attention is paid to exact finishing of the protheses. A smaller curvature of the prothesis and a safer distance between prothesis and cornea are recommended. The consensus is that the length of a prothesis ought to fit as close to the diameter of the anterior chamber as possible. However, it is extremely difficult to measure the diameter of the anterior chamber, and some uncertainty as to the correct length of a prothesis is therefore unavoidable (Maria, et al.). Several surgeons recommend having protheses of various lengths

Fig. 3 (Binkhorst). Tissue defect in the anterior chamber angle in a case of late corneal edema after implantation of an anterior chamber lens, with rigid supports in the chamber angle. (Photomicrograph of Dr. W. A. Manschot.)

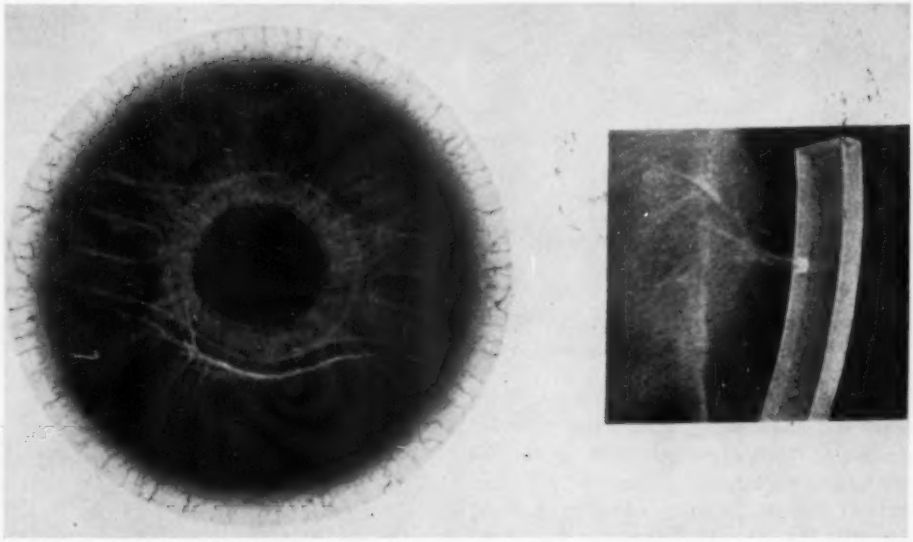

Fig. 4 (Binkhorst). Damage of the cornea due to an anterior chamber lens with rigid supports in the chamber angle. (Drawing, courtesy of the Department of Ophthalmology, University of Ghent, Ghent Belgium, director, Dr. Jules François.)

ready and determining the desired length during the operation (Barraquer, Ridley). Obviously this is not an ideal solution. Others choose purposely a prothesis which is too long, and insert the edges between sclera and ciliary body (Strampelli). It even seems that Parry does not hesitate to penetrate the sclera with the edges, placing them subconjunctivally.

In this connection should be mentioned the intraocular lenses of Dannheim, which are supported by the anterior chamber angle via loops of thin and flexible Supramid wire. These protheses, if not chosen too long, adapt themselves better to the diameter of the anterior chamber, and less damage may be expected from their contact in the chamber angle. My own experience with nine implantations of lens protheses of this type is still too recent to allow any definitive conclusions. It was noted, however, that complaints of hypersensitivity of the eye to touch are less common with the Dannheim protheses than with the rigid ones. The rather unpredictable position of the optic part in the anterior chamber is a disadvantage, however.

### C. The pupillary or iris clip lens (fixation and centering of the lens prothesis by the iris)

It seems that any possibility of contact with the anterior chamber angle and the posterior surface of the cornea should be avoided. For this purpose I designed a lens to be supported entirely by the iris diaphragm, having only minimal contact with the anterior and posterior iris surfaces.

*Description of the pupillary lens.* The optic part consists of a biconvex lens which can be made to individual specifications. It has a diameter of five mm. and is at its center 0.6-mm. thick. The material is polymethylmethacrylate, which is very light (S.G. 1.19), so that the lens weighs only 6.0 mg. in air. This lens has to be located immediately in front of the pupil, and in order to fixate it in this position it is provided with two wire loops, bent at right angles and attached to its posterior surface close to the equator.

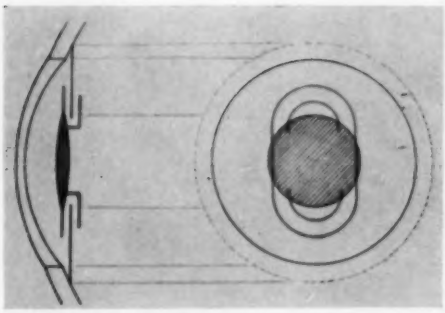

Fig. 5 (Binkhorst). Diagram, showing the fixation of the pupillary lens (iris clip lens).

These wire loops are inserted through the pupil and come to lie against the posterior surface of the iris, without reaching the ciliary body however, the distance between the ends of these loops being only seven to eight mm. (fig. 5). The attachments of these posterior loops are 0.5 mm. away from the equator and thus form a square, the diagonals of which are about four mm. long.

The posterior loops prevent a forward displacement of the lens. When the pupil is constricted around the attachments of these loops its form is more or less square. Luxation backward, through the pupil, is impossible then because the diameter of the optic part itself is five mm. However, in order to prevent luxation of the lens backward with a wider pupil, two flat wire loops have been mounted to the equator of the lens, increasing the greatest diameter of the part in front of the pupil to about eight mm.

The anterior loops are adjacent to the anterior surface of the iris, keeping a safe distance from the anterior chamber angle. The clearance between the anterior and posterior loops is 0.5 to 0.75 mm., just enough to enable the iris to slide in between. The loops consist of elastic Supramid wire, 0.1-mm. thick, a synthetic material which is equally well tolerated by the eye as the polymethylmethacrylate. I chose these wire loops for the fixation of the optic part because I consider it most essential to keep the total weight as low as possible and limit the contact with the iris to a minimum. As already mentioned, there is no contact with the anterior chamber angle. Moreover, as the lens is contiguous to the iris diaphragm, a greater and safer distance from the corneal endothelium is attained than with the usual anterior chamber lenses with fixation in the chamber angle.*

As to the centering of the pupillary lens, it should be pointed out that with a normal pupil of about three mm. the iris will support all four insertions of the posterior loops to an equal extent, resulting in an automatic centering of the lens by the sphincter pupillae muscle.

*Advantages of the pupillary lens.* Obviously the pupillary lens has the same advantages over the Ridley lens as the anterior chamber lens, which made the latter popular and the Ridley lens obsolete: simple operation technique, implantation at least several months after the cataract extraction, adaptation of the dioptric power to individual specifications, impossibility of luxation, and so forth. Moreover, the pupillary lens has some distinct advantages of its own:

1. As the lens is centered in front of the pupil by the sphincter muscle itself, an ideal position is always attained, even in cases with an eccentric pupil. Neither with the Ridley lens, nor with the usual anterior chamber lens, can such an exact centering be assured. A slight deviation from the ideal length of the latter may interfere with the desired centering.

2. One is independent of the diameter of the anterior chamber, which avoids the difficulties in determining the so-called ideal length of the usual anterior chamber lens.

3. One is also independent of the configuration of the anterior chamber angle. Peripheral anterior synechias, which add to the difficulties in determining the ideal length of

* The pupillary lens (iris clip lens) is manufactured by K. Morcher, Reinsburgstrasse 91, Stuttgart, Germany.

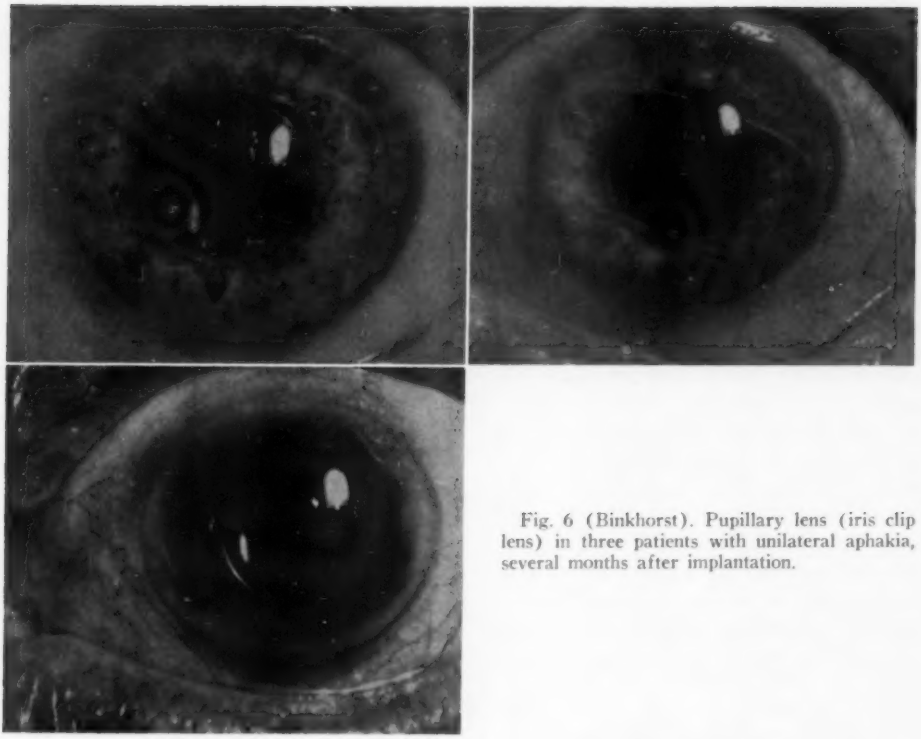

Fig. 6 (Binkhorst). Pupillary lens (iris clip lens) in three patients with unilateral aphakia, several months after implantation.

the usual anterior chamber lens, or even make its implantation impossible, will mostly form no contraindication to the insertion of a pupillary lens.

4. There is no potential danger of late corneal edema. As the pupillary lens does not have any contact with the anterior chamber angle, it cannot cause decubitus in this region. Neither can contact with the central part of the cornea result from deformation of the anterior segment of the eye, as the pupillary lens is at a greater distance from the cornea than the usual anterior chamber lens.

5. The retinal image size is more physiologic than with the usual anterior chamber lens.

6. If desired, the pupillary lens can be implanted in the not full-grown eye.

*Limitations of the pupillary lens.* There are also some specific limitations to the use of the pupillary lens, which are all related to conditions of iris and pupil. The pupil may not allow the insertion of the posterior loops, or might permit luxation of these loops later on. In this connection may be mentioned: (a) rigidity of the sphincter pupillae muscle, (b) adhesions of the posterior surface of the iris to the anterior limiting layer of the vitreous, as may occur following intracapsular extraction, or to capsular remnants after extracapsular extraction, (c) too wide a pupil (special consideration should be given to the size of the pupil in the dark), (d) large and total colobomas of the iris.

Since June, 1958, implantations of pupillary lenses were performed in 29 patients with unilateral aphakia. The results so far indicate that this form of fixation is well tolerated (fig. 6).

Without going into details of the method, we may state that no great technical difficulties are encountered in the implantation of a pupillary lens.

For the sake of completeness it should be mentioned that, after the development of the described lens prothesis with fixation by the iris, the same principle of fixation has been thought of elsewhere as well, although in an entirely different form. Schillinger and others published the results of implantations in animal eyes of intraocular lenses with a deep groove at the equator. With the exception of one reasonably good result all experiments were failures (luxation, corneal edema, and so forth). Epstein (Johannesburg) implanted similar lenses in aphakic human eyes. He calls them "collar-stud" lenses. These lenses are much heavier and bulkier than the described pupillary lens, and can best be classified as Ridley lenses with a modification to prevent luxation backward. They do not give the advantage of secondary implantation either, as they have to be inserted immediately following the cataract extraction.


## Summary

The results of a follow-up examination of 12 patients with a Ridley prothesis are discussed.

A group of 35 patients with anterior chamber lenses with rigid supports in the chamber angle were submitted to a critical evaluation at various times after the implantations. It appeared that in one fourth of these cases, approximately between six and 12 months after implantation, a late complication occurred, consisting of corneal edema due to mechanical damage.

A new method of fixation is presented in which the chamber angle is avoided and the possibility of contact with the corneal endothelium is eliminated, which makes the above mentioned complication impossible, while contact with the iris is limited to a minimum. The so-called pupillary lens or iris clip lens was successfully used in 29 patients.


*54 Axelsestraat.*

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# PLAIN VERSUS CHROMICIZED CATGUT SUTURES IN CATARACT SURGERY*

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In 1956 we evaluated and reported in The Journal 100 cataract extractions in which mildly chromicized buried 6-0 catgut was used for corneoscleral wound closure.[1] We felt that this type of suture, when buried beneath a conjunctival flap, was well tolerated, gave a tight closure of the wound, by that reducing postoperative astigmatism, and avoided the hazards associated with the removal of silk sutures. The fact that the sutures were entirely covered by a conjunctival flap all but eliminated the possibility of epithelial downgrowth along the suture track.

As our experience with buried chromicized catgut sutures increased, one annoying occurrence was noted in about 15 percent of the cases.[2] If the conjunctival flap is very thin, one or both sutures may gradually perforate the flap, protrude over the surface, and, by that, nullify the desired effect of the conjunctival coverage. This is obviously due to the fact that the chromicized catgut sutures are not completely absorbed for several weeks. While this does not matter as long as the sutures remain covered by the conjunctival flap, if the conjunctiva is pierced, the very purpose of the technique is defeated. The presence of uncovered sutures not only causes irritation to the patient, but, due to the exposure, it affords the chance for epithelial downgrowth and the possibility of infection along the suture track.

In order to avoid this complication, we decided to try plain 6-0 catgut sutures for corneoscleral closure. As these should be absorbed much faster than mild chromic 6-0 catgut, there should be less danger of their persisting and eroding through the conjunctival flap.[2]

It is the purpose of this paper to report our experience with plain 6-0 catgut sutures buried under a conjunctival flap for corneoscleral wound closure in cataract extractions and to compare the results with those previously reported with mildly chromicized 6-0 catgut sutures.

A straight series of 130 cataract extractions performed on 117 patients by one of us (F. W. S.) at McPherson Hospital was analyzed. The longest period of observation for any patient was over two years, the shortest, three months.

The technique of cataract extraction was identical with the one previously described,[1] the only difference being the use of plain instead of mildly chromicized 6-0 catgut.*

The results as compared with those of the series in which chromicized catgut had been used are summarized in Table 1.

With regard to the frequency of anterior chamber hemorrhages, iris prolapse, delayed formation of anterior chamber, late loss of anterior chamber and late shallowing of anterior chamber, the two series were in surprising accordance. The percentage figures are almost identical.

As expected, erosion of the plain catgut sutures through the conjunctival flap was encountered considerably less frequently (three percent) than it had been with the chromicized catgut sutures (15 percent). This obviously was due to the more rapid absorption of the plain sutures. In fact, in 34 of the 42 patients in which notations on the time of disappearance of the corneoscleral sutures were available, the sutures had completely disappeared by the 12th day. In the remaining eight cases, the sutures disappeared between the 13th and the 40th day.

On the other hand, as suspected, the total average astigmatism was slightly higher with plain catgut (1.47 diopters) than with chro-

* From the McPherson Hospital.

* Ethicon B-770. Micropoint cutting Atraloc G-1 plain 6-0 catgut was used.

TABLE 1

COMPARISON OF CHROMIC CATGUT AND PLAIN CATGUT

| Complication or Result | Chromic 100 Cases | Plain 130 Cases |
|---|---|---|
| Anterior chamber hemorrhages | 20 (20%) | 30 (23%) |
| Iris prolapse | 1 (1%) | 1 (0.8%) |
| Delayed reformation of ant. cham. | 0 (0%) | 0 (0%) |
| Erosion through conjunctival flap | 15 (15%) | 4 (3%) |
| Late loss of ant. cham. | 1 (1%) | 1 (0.8%) |
| Late shallowing of ant. cham. | 3 (3%) | 4 (3%) |
| Total average astigmatism | 1.06 D. | 1.47 D. |
| Astigmatism with the rule | 47 (47%) | 29 (22%) |
| Astigmatism against the rule | 31 (31%) | 84 (64%) |
| No astigmatism | 22 (22%) | 17 (14%) |

micized catgut (1.06 diopters). Also, there were relatively more cases with astigmatism against the rule with plain (64 percent) than with chromicized catgut (31 percent). Probably the plain catgut becomes absorbed before the wound is healed firmly enough not to stretch. Nevertheless, the majority (81.6 percent) of patients had postoperative astigmatism within the range from 0.0 to 2.0 diopters, whereas only six (4.6 percent) showed astigmatism greater than three diopters (table 2).

As can be seen from Table 3, the visual results on the whole were quite satisfactory. Only 22 cases (16.9 percent) obtained vision of less than 20/30. The reasons for the reduced vision in these cases were found to be in no way connected with the suture material or, for that matter, with factors of technique in general (table 4).

With regard to the occurrence of hyphemas, we should like to emphasize again

TABLE 2

AMOUNT OF POSTOPERATIVE ASTIGMATISM

| Diopters | Number | Percent |
|---|---|---|
| Less than 1 diopter | 32 | 24.6 |
| 1 to 2 diopters | 74 | 57.0 |
| 2 to 3 diopters | 18 | 13.8 |
| Greater than 3 diopters | 6 | 4.6 |
| TOTAL | 130 | 100.0 |

Total average astigmatism 1.47D.

TABLE 3

POSTOPERATIVE VISUAL RESULT

| Vision | Number | Percent |
|---|---|---|
| 20/30 or better | 108 | 83.1 |
| 20/40–20/70 | 14 | 10.8 |
| 20/80–20/100 | 3 | 2.3 |
| 20/200 | 1 | 0.8 |
| Less than 20/200 | 4 | 3.0 |
| TOTAL | 130 | 100.0 |

as in the previous paper[1] that, for the purpose of these reports, even the smallest amount of blood present in the anterior chamber was considered as an anterior chamber hemorrhage. This may account for the relative high incidence as compared with some other reports. Nevertheless, we cannot exclude the possibility that the catgut may be responsible for some of the hemorrhage as predicated by Dunnington and Regan.[3] The main point is that all hyphemas cleared without interference with the final visual result.

Prolonged persistence of edema of the conjunctival flap should be mentioned as a complication noticed in seven cases (five percent). Cystic enlargements around the sutures were present in four cases. Probably these instances were due to tissue reaction to the suture material rather than to an actual leak. These complications, however, eventually subsided in all instances except in one case in which a filtering bleb had to be repaired. This did not affect the final visual result.

There was only one case of postoperative glaucoma and no instance of postoperative infection.

TABLE 4

CAUSE OF REDUCED VISION AFTER CATARACT EXTRACTION

| | |
|---|---|
| Senile macular degeneration | 8 |
| Congenital defects (nystagmus, etc.) | 4 |
| Vitreous opacities | 3 |
| Primary glaucoma | 3 |
| Secondary membrane (after needling) | 1 |
| Unexplained | 3 |
| TOTAL | 22 |

## Discussion

While Davis,[4] Hughes, Guy and Romaine,[5] Alger[6] and others had reported satisfactory results with plain catgut in cataract surgery using different techniques, Dunnington and Regan,[3] Roberts,[7] ourselves[1] and others advocated mildly chromicized catgut. We had thought that the slow absorption of the chromicized catgut sutures would not matter if they were buried under a conjunctival flap. After analyzing the results of the present series, we now feel that plain catgut is perfectly adequate for the corneoscleral sutures in cataract surgery. The initial closure of the wound may not be quite as tight as suggested by the slightly higher degree of postoperative astigmatism, but the final results are comparable with those obtained by mildly chromicized catgut. The fact that plain catgut sutures show a much lower incidence of erosion through the conjunctival flap enhances the desired effect of our technique. Furthermore, due to the faster disappearance of plain catgut sutures, there is less irritation and discomfort during the postoperative course.

Weighing the advantages against the disadvantages, we are inclined to give preference to plain 6-0 catgut for corneoscleral sutures in our technique of cataract extraction with absorbable sutures buried under a conjunctival flap.

## Summary

A series of 130 cataract extractions, in which 6-0 plain catgut buried corneoscleral sutures were used, is reviewed and compared with a series previously reported in which 6-0 mildly chromicized catgut was used. Adequate closure is obtained with rapid absorption of suture material, giving the advantages of less irritation to the patient and less chance for erosion through the conjunctival flap. There is slightly more postoperative astigmatism with plain catgut than with mildly chromicized catgut, but the difference is so small as to be negligible. Plain catgut sutures covered by a conjunctival flap are recommended for the closure of the cataract section.

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# PROGRESSIVE ESSENTIAL IRIS ATROPHY

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Although unilateral progressive iris atrophy is relatively uncommon, a number of such cases have been reported in the literature. On the other hand, bilateral essential iris atrophy is extremely rare and the reported cases can actually be counted on one's fingers.

Several authors, including Duke-Elder[1] have emphatically stated that essential iris atrophy is a disease which involves only one

eye, yet the few reported cases of genuine bilateral essential iris atrophy are evidence that such a view does not hold absolutely true. This communication is intended to report two cases of this disease, one of which is bilateral. Reference will be made to the histopathologic findings, the theories which have been presented to explain the development of the atrophy in the iris, and the relationship of this process to glaucoma.

A new concept[2] was offered in a report in 1951 based on a study of two patients in the Eye Clinic of the University of Bonn. The first of these two patients had bilateral iris atrophy with formation of holes, as well as another etiologically obscure clinical entity—myotonia atrophica or Curschman-Steinert disease. The second case had myotonia atrophica together with advanced iris atrophy—holes were not seen. The two cases to be reported in this communication were studied for the purpose of evaluation of the relationship between iris atrophy and myotonia atrophica. The clinical and laboratory findings will be described.

## Terminology and historical review

Since the formation of a hole in the iris pseudopupil (real pupil should be surrounded by sphincter pupillae muscle) is one of the most important clinical findings of essential iris atrophy, such terms as the following are, in the old literature, very often related to essential iris atrophy: corectopia, polycoria, diplocoria, tricoria, coloboma of the iris, dehiscence formation in the iris and unilateral pupil doubling. The more modern terminology includes essential progressive iris atrophy, spontaneous iris hole formation, and irideremia. At the present time the term progressive essential iris atrophy is being appropriately used in preference to all others.

This confusion in terminology makes it easy to understand why several cases have been reported in the literature under the title of essential iris atrophy where they actually do not belong. Harms[3] (1903) presented the first clear-cut description of essential iris atrophy, thus giving the basic outline of our understanding of this clinical entity. Lohlein,[2] in his extensive study in 1951, found that of 50 authors who presumably have presented reports on this disease only 20 of them actually dealt with genuine cases. Cases of secondary iris atrophy resulting from one cause or another represented the majority of these 30 equivocal reports.

It is quite evident that atrophy of the iris can be the end-result of numerous inflammatory and/or degenerative processes within the eye, and a hole formation would only indicate an extreme phenomenon of such an atrophic process. It is, therefore, important to emphasize that the term "progressive essential iris atrophy" must be restricted to those cases in which careful clinical examination of the eye in general and the anterior segment in particular fails to show an evident etiologic factor.

Increased intraocular pressure, chronic or acute iritis, chronic or acute iridocyclitis, trophic changes of phthisis bulbi, and even senility are among the etiologic factors that may lead to secondary atrophy of the iris. Furthermore, traumatic insults to the anterior segment of the eye may lead to secondary iris atrophy. An injury may result in a rupture or occlusion of the iris vessels which originate from the major iridic circle. Such vascular damage is often seen in traumatic iridodialysis, traction of the iris tissue after its incarceration in a corneal scar, and after traumatic hemorrhage.[4] Iris atrophy is often seen in connection with siderosis bulbi.

Among the doubtful cases in the literature is Johnson's[5] case (1886). Johnson reported a patient who had lost one eye because of an accident 18 years prior to the development of extensive iris atrophy of the other eye. The author failed to state whether or not any signs of inflammation were present, nor did he mention anything about the intraocular pressure. Hess[6] (1892) reported a case in which the pupil was displaced to the temporal side, and a large gap or hole

in the iris was reported in both eyes. There was bilateral deep cupping and elevated intraocular pressure. It was thought that the iris atrophy was the result of chronic iridocyclitis because of the presence of small white spots on the capsule of the lens. Fine and Barkan's[7] case of a nine-year-old boy (1937) is also equivocal. This was thought to be a case of congenital glaucoma as the first recorded tension was 60 mm. Hg, R. E.; 50 mm. Hg, L.E. The left eye later showed clinical manifestations of buphthalmos.

### Essential iris atrophy and biomicroscopy

Since the chances of obtaining histopathologic material from human eyes early in the course of this disease (before the development of glaucoma) are practically nil, careful biomicroscopic examination seems to be invaluable for the study of such cases. Repeated slitlamp examination with inquisitive observation may conceivably throw light upon the questions which have so far remained unanswered.

Iris atrophy may predominantly affect the stromal or the epithelial layer. However, the involvement of these two layers may be equally distributed.

In stromal atrophy, the iris pattern, the collarette, and the crypts become very poorly distinguished.[8] The anterior surface of the iris becomes flattened and smooth as a result of diminution in the thickness of the mesodermal layer. The trabecular strands, which are normally fluffy and bluish brown in color, look compact and yellowish white. In their radial course on the surface of the iris these strands take a more or less straight pattern. Because of the absence of the binding stromal tissue on the anterior surface of the iris the trabecular strands become separated from one another. The crypts lose their circular shape and take an elongated outline and later form deep gutters at the bottom of which the pigmented epithelium can be seen.

Red blood vessels are occasionally noted originating from the peripheral zone of the iris and extending radially to the pupillary margin or to the region of the lesser iridic circle. The diminution of the pigment elements in the iris stroma makes it easier to see the outline of the sphincter pupillae. The iris is occasionally seen to be fibrotic, thickened, and shrunken, thus pulling the pigment layer forward over the pupillary border, producing ectropion pupillae.

The loss of the pigment on the surface of the iris may take place in multiple localized areas which appear whitish gray in color, a condition described as vitiligo iridis.[4]

These findings can be more easily illustrated in light or bluish irises where the stromal tissues are loose and contain a minimal amount of pigment granules. An optical section can be observed, if a narrow beam of light from a slitlamp is used.

The atrophic changes in the ectodermal pigment layer of the iris result in loss of pigment in the form of streaks and patches. These atrophic areas can best be demonstrated by transpupillary retro-illumination. They appear yellowish red in color as they transmit the rays of light reflected from the fundus. Direct focal illumination is, as a rule, not adequate to demonstrate these defects in the pigment layer, especially in dark or brown eyes, because of the dispersion of light by the melanophores of the stromal layer. A similar process is often seen in older people where the pupillary border by this type of illumination looks moth eaten because of the absence of the pigment in areas adjacent to the pupil.

It cannot be overemphasized that, biomicroscopically, the atrophic changes in progressive essential iris atrophy do not basically differ from those in iris atrophy of any other origin. However, it is the absence of posterior synechias, keratic precipitates, pigment and fibrin deposit on the anterior surface of the lens, and other stigmas of inflammation of the anterior segment of the eye which would determine that such cases are actually of an essential type.

## Essential iris atrophy and gonioscopy

Gonioscopy is as important a device as biomicroscopy in the clinical study and follow-up of this condition. It should[9] be performed together with careful slitlamp examination at regular intervals in order to explore the extent and nature of the changes in the iris, the anterior chamber angle, corneoscleral trabeculae, and peripheral part of the cornea. This segment of the eye is of particular interest in the disease because of the eventual development of glaucoma.

The first report in the literature of a gonioscopic study in a case of essential iris atrophy was presented by Troncoso in 1937. The patient was a 29-year-old nurse (McKeown reported case[9]). Troncoso stated that the anterior stromal layer of the iris was atrophic and drawn toward the angle of the chamber by new tissue which had a compact, fibrous appearance, a yellowish color, and fastened the iris to the limbus, producing a wide peripheral anterior synechia. On either side of the synechia, the angle was open. Troncoso had also noticed that the retinal layer of the iris had been drawn upward toward the cornea at the angle and appeared as a sheet of brown color raised to the transparent edge of the limbus.

Since that report, Sugar,[10] Daily and Daily,[11] and Lohlein,[2] have presented clear descriptions of their gonioscopic findings. Their reports differ little from Troncoso's. Lohlein emphasized that the angle and the corneoscleral trabeculae showed no pigment deposition. He demonstrated, as Troncoso did, a detachment of the iris and its reattachment to the scleral trabeculae and posterior surface of the cornea. His examination was repeated after six months and the findings were the same. Sugar found an area where the anterior synechia extended slightly to the back of the cornea. He also demonstrated a mesodermal network bridging portions of the angle recess, with a large vessel on its surface.

## Course of disease and clinical findings

Essential iris atrophy is an uncommon disease. Czukrasz[12] stated that in the University Eye Clinic, Debreçen, only two cases had been seen in an interval of 25 years. In my two-and one-half years residency training at Bellevue Hospital, I saw only one case. Amazingly enough, I saw the two cases to be reported in this communication within one week.

Essential iris atrophy is a disease of young adults. The average age of onset is 30 years (Henderson and Benedict[13]) but it has been reported in a patient as young as five years, and one as old as 54 years. It occurs more frequently in females than in males. It has, as a rule, an insidious onset.

The first stage is characterized by symptomless displacement of the pupil (corectopia). With its displacement the pupil usually becomes pyriform in shape, the narrow end pulled to the limbal area. The part of the iris diagonal to this shows stretching of its fibers and later a break in continuity of the stromal and pigment layers.

That the displacement and pyriform shape of the pupillary opening is not an integral part of this disease is demonstrated by Case 2 in this report. The pupils in this case were more or less circular and centrally located in front of the axial part of the crystalline lens.

In this disease the atrophic changes are more often seen at the peripheral zone of the iris, and the central pupillary zone is, as a rule, the last and least to be involved.

There is a difference of opinion as to which layer of the iris shows the earlier changes—the stromal or the pigment. Some reports indicate an early loss of the stromal layer, while others indicate the pigment layer. Still others point out almost simultaneous atrophic changes of two layers. The findings on the two patients to be reported here are in favor of the belief that the changes start earlier and become more advanced in the stromal layer.

The second stage of the disease is distinguished by the development of holes in the iris diaphragm. There may be one, two, or more holes of different shapes and sizes. Sometimes, these multiple holes coalesce to form a large defect in the iris. At this stage some of the iris trabeculae may become loose and float freely in the anterior chamber whenever the position of the head is changed. It is often observed that the intimate adherence of the stromal and pigment layers no longer exists.

The third and last stage is characterized by the development of glaucoma which is secondary in type and of gradual onset. Outflow studies of my two cases revealed a low facility of a degree proportionate to the extent of blockage of the corneoscleral trabeculae by the goniosynechia. This secondary glaucoma usually does not respond to medication and surgery is not always effective in reducing the intraocular pressure. Such eyes, by and large, after a length of time, lose field and become blind and painful, necessitating enucleation.

## Histopathology

Of all the histopathologic studies on this disease there is not a single case that has been fully examined before the development of glaucoma. Increased intraocular pressure in itself is certainly a major factor in producing atrophy in the uveal tract; consequently, the data so far available is by no means purely illustrative of the processes active in the early cases of essential iris atrophy.

Daily and Daily's report (1957)[11] on a biopsy from the iris tissue before the development of glaucoma is probably the only demonstration of the histopathologic manifestations of the iris in the early stages of this disease. This report, however, is of limited instructive significance because it does not include the other parts of the eye, such as the ciliary body, the angle, the corneoscleral trabeculae, and the peripheral portion of the iris.

Heath[14] (1954) presented a comprehensive histopathologic study and his findings are of great interest. Heath's 10 cases are presumably of advanced glaucomatous eyes which had been enucleated and kept in the eye pathology laboratory of Massachusetts Eye and Ear Infirmary and the Armed Forces Institute of Pathology. His histopathologic sections clearly demonstrate that the spotty atrophy of the iris tissue is the result of reduction in the lumen of the smaller arteries, produced by hyaline thickening of their walls. This was responsible for anemic infarcts. The cause of these vascular changes is not yet known.

Heath was able to demonstrate surviving islands of iris stroma in the vicinity of an open vascular channel, within a widely atrophic patch. The sectors which had open or patent arteries and capillaries showed surviving iris stroma, sphincter and dilator muscles, and pigment layer. Endothelized cuticular membrane was demonstrated in five of his 10 cases. This membrane extended from the cornea and covered the corneoscleral trabeculae, as well as the peripheral anterior synechia. This membrane, together with the peripheral anterior synechia, loss of the resorption capacity of the iris, and the blockage of the angle by the debris of the iris, constitute the mechanism of secondary glaucoma.

The other histopathologic reports[15, 16] stress presence of extensive peripheral synechia with atrophy of the iris tissue in a rather irregular pattern.

## Case reports

### Case 1

H. A., a white man, 26 years of age, was seen for the first time on October 28, 1958. He stated that he had his first eye examination and first pair of glasses, two and a half years ago, because his eyes felt tired on reading and writing. Eyedrops were used in the process of examination and, six months later, he noticed that his left pupil was

Fig. 1 (Gazala). *Case 1.* Essential iris atrophy of the left eye. The iris is normal in the right eye.

irregular and displaced downward. This he thought was caused by the eyedrops used in that examination. Five months later he noticed that the upper part of the iris was split in the middle. There was no history of headaches or difficulty in seeing for distance or near. As far as he could remember there was no trauma or inflammatory episodes, acute or chronic, in either eye. He had been married for three years without progeny.

Physical examination and laboratory work-up to determine the cause of sterility revealed that he had complete aspermia of no apparent etiology. Interrogation disclosed that since his marriage he has been as sexually active as the average male of his age. On both sides of his family there has been no history of sterility or any eye problem. He has never experienced a delayed relaxation or weakness of the skeletal muscles in warm or cold weather (delayed relaxation of myotonia atrophica can be elicited more easily in cold weather).

Examination revealed a healthy male of normal development and intelligence. There was no frontal baldness but his beard was so sparse that he did not have to shave more than twice a week. His chest and pubic hair was also sparse. The testicles and penis were of average size. The muscles all over the body showed no wasting or weakness. The tendon reflexes were normal. There was no delayed rigidity in the fists or any other group of muscles.

*Eye examination.* Visual acuity in the right eye was 20/20; left eye, 20/30. Refraction revealed an error of +0.25D. cyl. ax. 85°, right eye, and +0.5D. cyl. ax. 85°, left eye. With this correction his visual acuity was 20/20 in each eye.

*Right eye.* Examination was essentially negative except for a few faint dotlike lens opacities in the nuclear zone. Careful slitlamp and gonioscopic study revealed normal findings (fig. 1).

*Left eye.* Examination revealed adnexa, lids, conjunctiva and sclera to be within normal limits. Slitlamp examination revealed a clear normal cornea.

The pupil was pyriform in shape with its narrow end displaced down to a point about two mm. from the limbus at the 7-o'clock position (fig. 2). The sphincter pupillae could be seen all around the pupil, including its lower narrow end. The pigment seam was of normal width except at the lower part where it showed ectropion pupillae of about two mm. The pupil reacted well to direct and consensual lights. With 10-percent Neosynephrine and one-percent Pilocarpine, the lower part of the pupil was found to be fixed but the rest of the pupil dilated and constricted readily.

The sector of the iris between the 1-o'clock and 9-o'clock positions showed four triangular defects in the iris stroma. In the areas at the 1-o'clock and the 12-o'clock positions, there was also a defect in the pigment epithelial layer through which the lens capsule, and the zonular fibers and their attachments to the equator of the lens could be easily seen. The two other defects in the stroma showed no changes in the pigment layer.

It was noted that dehiscence in the stromal and pigment layers extended as far down as the upper border of the sphincter pupillae. A few blood vessels could be seen at the border of the atrophic patches. It was evident that there were no posterior synechias, keratic precipitates, or any stigmas of an inflammatory process, fresh or old.

*Gonioscopic study* disclosed a localized peripheral anterior synechia in the area adjacent to the atrophic iris. The most peripheral part of the iris, corresponding to the holes at the 1-o'clock and 12-o'clock positions, seemed to have been pulled forward and become adherent to the posterior surface of the cornea and the corneoscleral trabeculae. These areas appeared dark brown in color as they displayed the pigment epithelium of the iris.

Blood vessels in the form of fine networks were seen on the surface of the peripheral iris tissue remnants. The anterior surface of the lens, the lens equator, the zonule, and the ciliary processes which were seen through the iris holes were all of normal size, shape and color. The angle on both sides of the wide anterior synechia was open and free except for an area at about the 1-o'clock position where the angle was narrow because of thickened stromal tissue at the periphery of the iris.

The lower part of the angle at the 7-o'clock posi-

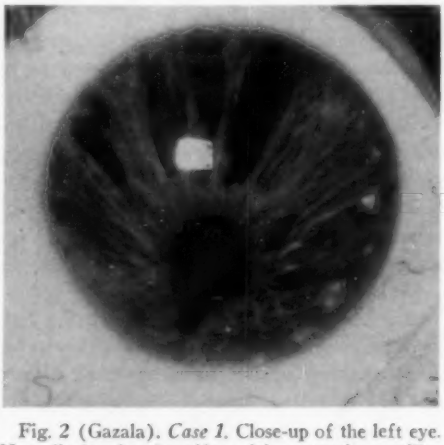

Fig. 2 (Gazala). *Case 1.* Close-up of the left eye. Note displaced and pyriform iris; ectropion pupillae at about the 7-o'clock position, extensive atrophic area from the 1-o'clock to 8-o'clock positions. The areas at the 1- and 12-o'clock positions show atrophy of both the pigment and the stromal layer. The rest shows stromal atrophy alone.

Fig. 3 (Gazala). *Case 1.* Electrotonographic record done on November 10, 1958. Facility of flow right eye 0.14, facility of flow left eye 0.073.

tion, where the narrow end of the pear-shaped pupil was located, was found to be completely closed. The iris stroma was thickened and adherent to the corneoscleral trabeculae, Schwalbe's line and part of the posterior surface of the cornea. This anterior peripheral synechia extended from the 5-o'clock to the 8-o'clock positions.

Tonography was done using Mueller electrotonometer and Sanborn-Twin-viso recording unit, and was repeated six weeks later (figs. 3 and 4). The following data were obtained:

| | | | |
|---|---|---|---|
| 11-10-58 | O.S. (1st) | P.O. −18.80 | C. −0.0731 |
| | O.D. (2nd) | P.O. −11.34 | C. −0.14 |
| 12-22-58 | O.S. (1st) | P.O. −18.80 | C. −0.0536 |
| | O.D. (2nd) | P.O. − 9.53 | C. −0.23 |

*Laboratory studies* done on his admission to the Medical College of Virginia Hospital on February 9, 1959 showed: Hemoglobin 15.4 gm.; W.B.C. 5,600; urinalysis, normal; fasting blood sugar, 76 mg. percent; blood urea nitrogen, 14 mg.; serum electrolyte studies reveal sodium of 141 meq./liter; postassium, 4.3 meq./liter; chlorides, 101 meq./liter; $Co_2$, 26 meq./liter. Serology was negative. Chest X-ray films revealed prominent bronchovascular markings but were otherwise negative. Electrocardiogram revealed sinus arrhythmia. Urine 17, hydroxycorticoids were well within normal limits on two days' collection.

CASE 2

C. R., a 26-year-old Negress, was seen in the Medical College of Virginia Hospital emergency room for the first time on September 6, 1958. She was brought in an ambulance because of a black-out episode in the street while doing some shopping. She claimed that she had been having such episodes occasionally over the past two years. These episodes, she said, usually started as a feeling of warmth all over her body, followed by complete darkness, and weakness to the point of falling to the ground. She had never had complete loss of consciousness as she could always hear people around her. Within 20 to 25 minutes these spells came to an end but a feeling of weakness persisted for an hour or two afterward. There was no mention of convulsions, nausea, vomiting, or loss of sphincter control. She had been married for three years but never became pregnant. Her menstrual periods were normal as for the amount of flow and regularity.

*On physical examination* she was found to be a well-nourished and well-developed female of subnormal intelligence. No wasting of the muscles or myotonicity could be elicited. The breasts and genitourinary system were normal. There were no significant findings other than the presence of holes in the iris of both eyes (fig. 5). She was, therefore, sent to the Eye Clinic for evaluation on November 3, 1958. Her visual acuity was: R.E., 20/30, correctible to 20/20 with a −0.5D. cyl. ax. 45°; L.E., 20/20, with no significant refractive error.

*Right eye.* The adnexa, lids, conjunctiva, sclera, and cornea were within normal limits. The anterior chamber was deep and there were no keratic precipitates, flare, or cells. The pupil was more or less round and centrally located.

The iris showed a patch of atrophy at the 3-, 6- and 9-o'clock positions, each about 2.5 mm. in diameter (fig. 6). The atrophic patch at the 3-o'clock position showed a hole in the entire thickness of the iris tissue through which the lens could be seen, as well as the fundus. The apparent defect in the pigment and stroma was actually the result of a nasal displacement of the pupillary border of the pigment layer as the remnants of the excrescences and crevices of the pigment seam could be seen on the nasal side of the iris hole. The temporal border of the hole consisted of a thin atrophic strip of the stromal layer of the iris with absence of the sphincter pupillae muscle.

The atrophic patch at the 9-o'clock position involved the stromal layer alone and it revealed a phenomenon of extreme interest. Because of the absence of the stromal layer of the iris in this area,

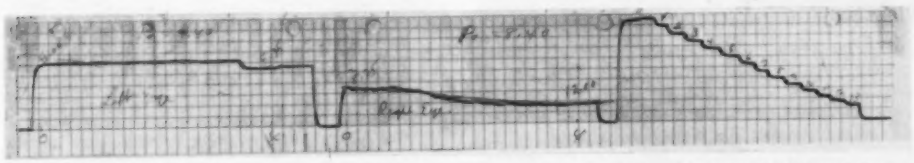

Fig. 4 (Gazala). *Case 1.* Electrotonographic record repeated on December 22, 1958. Facility of flow right eye 0.23, facility of flow left eye 0.53.

Fig. 5 (Gazala). *Case 2.* Bilateral essential iris atrophy.

it was possible to observe and study the movements of the pigment layer and the mechanical action of the dilator pupillae. The delicate pigment layer of the iris was seen to form a pouchlike depression with its concavity forward, when the pupil was dilated. It was evident that the action of the dilator muscle was mainly in a backward and outward direction. When the pupil constricted the concavity was flattened out. Moreover, the movements of the pigment layer in the atrophic patch were very free compared to the part of the iris which was covered by a stromal layer, as if the stroma was acting as a splint to check or diminish the movements of the pigment layer. The stromal layer definitely showed less elasticity than the pigment layer.

Careful slitlamp study of this atrophic patch under high magnification with indirect focal illumination revealed a few radial silver-gray shining streaks in the pigment layer which represented narrow linear atrophic areas through which the lens capsule was seen. By transpupillary retro-illumination, these gray streaks appeared orange red in color because of the fundus reflex. The lesion at the 6-o'clock position was basically the same as that at the 9-o'clock.

Neosynephrine (10 percent) was used for dilatation of the pupils. It was found that one drop in the right eye was enough to produce complete dilatation in less than 15 minutes. This was presumably due to weak or absent sphincter pupillae. On dilatation this pupil took a vertically oval outline. Pilocarpine (two-percent drops) was used to constrict the pupil, and it took about 90 minutes to produce moderate miosis. The pupillary opening, on miosis, appeared as a vertical slit two mm. wide and four mm. long. The shape of the pupil was again the result of absence of the sphincter muscle on the lateral and nasal parts of the pupillary opening.

The stroma in the relatively normal parts of the iris had a hyaline or gelatinous appearance because of the absence or diminution of the pigment granules. Some shreds of gray color, originating from the stromal layer, could be seen floating in the anterior chamber like fluffed cotton.

*Gonioscopy* revealed a definite anterior peripheral synechia adjacent and limited to the three areas of iris atrophy. The intervening parts of the angle were rather open and free. The rest of the eye examination was essentially negative.

*Left eye.* The adnexa, lids, conjunctiva, sclera, and cornea were negative. The iris showed an atrophic patch at about the 9-o'clock position where the stroma was absent except for a small strip in the area adjacent to the pupil (fig. 7). The pupillary seam of the pigment layer again seemed to have been displaced toward the limbus, producing a gap be-

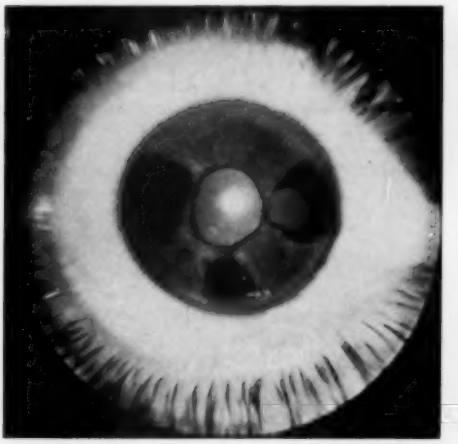

Fig. 6 (Gazala). *Case 2.* Right eye, transpupillary retroillumination. Note a more or less round pupil. A hole in the iris at the 3-o'clock position. The temporal border of the hole consists of an atrophic strip of iris stroma. The inner border is made of the stretched displaced pupillary border of the pigment layer. The atrophic process at the 6-o'clock and 9-o'clock positions involves mainly the stromal layer.

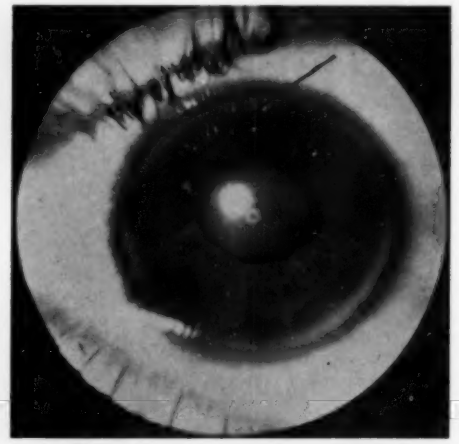

Fig. 7 (Gazala). *Case 2.* Left eye, transpupillary retroillumination. Note a small iris hole at the 9-o'clock position. This is the result of nasal displacement of the pupillary border of the pigment layer. Another hole not very clearly seen in this photograph (arrow) was present at the upper part of this atrophic patch. Prolapse of the iris pigment at the 2-o'clock position on the pupillary border.

Fig. 8 (Gazala). *Case 2.* Electrotonographic record made on November 19, 1958. Facility of flow right eye 0.16. Facility of flow left eye 0.25.

tween the pigment layer on the nasal side and the remnant of the stromal layer on the temporal side. At the periphery of this atrophic area, there was also a defect in the pigment epithelial layer through which the lens capsule could be seen. At about the 2-o'clock position on the pupillary opening there was a prolapse of the pigment epithelium of about 1.5 mm. in width.

*Gonioscopic examination* revealed an anterior peripheral synechia at about the 9-o'clock position.

Tonographic study was done on November 19, 1958 (fig. 8) and revealed the following:

O.S. P.O. −23.17 C. −0.23
O.D. P.O. −24.08 C. −0.16

The results of the laboratory examination done in the out-patient department were: X-ray films of the chest were negative. Urinalysis revealed specific gravity 1.016; albumin plus; blood sugar 68 mg.; R.B.C., 4,720,000; W.B.C., 11,800; hemoglobin 12.6 gm.; serology, nonreactive.

## Discussion

The etiology of essential iris atrophy poses a great challenge. Many theories have been presented but none is fully acceptable. Feingold[16] postulated that iris atrophy was the result of some vascular change of a congenital origin in the circulus iridis minor. Larson[17] thought the iris atrophy was the result of some obscure developmental anomaly beginning with corectopia. deSchweinitz,[18] stated that the iris atrophy was due to abiotrophy. Kreiker[19] presented an interesting theory based on an assumption that the processes responsible for the absorption of the pupillary membrane during the intrauterine life become, for unknown reasons, reactivated, resulting in absorption of iris tissue. Waite[20] was of the opinion that the atrophy of the iris was due to a mechanical stretching which caused narrowing of the iris vessels and in turn nutritional atrophy.

The association of this disease with other systemic manifestations was never significantly emphasized. Since this disease has a long, protracted course, it is evident that the systemic manifestations accompanying the eye findings are naturally considered coincidental. It was in 1951 that Lohlein[2] for the first time called attention to the relationship of essential iris atrophy and myotonia atrophica.

Myotonia atrophica is a familial disorder of multisystem involvement and obscure etiology. Contrary to general impression, the disease is fairly common and frequently unrecognized.[21–25] It is characterized by wasting and weakness of the muscles, delayed relaxation following voluntary contraction, congenital cataracts, testicular atrophy and ovarian hypoactivity. Other manifestations, such as frontal baldness, mental deficiency, occasional absence of the tendon reflexes, and various endocrinopathies may be associated.

Careful review of the cases of essential iris atrophy reported in the literature for any mention of signs and symptoms suggestive of myotonia atrophica was made. It was found that two reported cases of essential iris atrophy revealed some hereditary pattern. The first was a case reported by McKeown,[9] where the patient stated that her brother had the same eye condition. The second was reported by Rossano,[2] where both father and son had essential iris atrophy. Absence of the knee jerk, of unknown etiology, was mentioned in McKeown's[9] report and, because of that, the patient for a long period of time was unable to obtain life insurance. The following statement by Henderson and Benedict[13] may lead to the belief that the patient concerned had some testicular dysfunction.

They stated, "The patient came to Mayo Clinic for the purpose of having a general physical examination with particular reference to three complaints, namely, an irregular pupil of the left eye, indigestion of two years' duration associated with nervous tension, and discolored semen."

A report by deSchweinitz[26] (1915) may suggest myotonicity in the face muscles together with weakness of the other skeletal muscles. deSchweinitz reports: "Dr. D. J. McCarthy was called in consultation by her (patient's) family physician, Dr. Council, and writes thus concerning his investigation, '. . . There is a well-defined Chvostek symptom (hyperirritation of the seventh nerve on percussion) which in the absence of tetany is practically always an evidence of some intoxication and most frequently an intoxication from the gastrointestinal tract. I was not able, however, to find anything from physical examination to indicate any disturbance in this area. The blood pressure apparatus recorded systolic 120, diastolic 80 (Stanton apparatus). As a whole, the case rather impresses me as one of low tone, due to a latent glandular tuberculosis with chronic intoxication'."

The so-called Chvostek sign has been reported in several patients with myotonia atrophica. Waring, et al.[25] in their report of 13 patients with myotonia atrophica, have demonstrated a true positive Chvostek sign (contraction of the facial muscles by percussion of the facial nerve trunk) in one patient. Another patient showed a twitch which appeared to be due to facial muscle irritation rather than to nerve stimulation. A third patient had an equivocal Chvostek sign. These findings should give particular significance to deSchweinitz's report of a Chvostic sign in the presence of essential iris atrophy.

Another literature review was made of the reported cases of myotonia atrophica for any manifestations of essential iris atrophy. This review revealed no suggestion of iris atrophy, essential or otherwise, in any of the cases studied under the slitlamp. It is worth mentioning that many such cases were carefully studied by ophthalmologists to determine whether or not a congenital cataract was present.

It is concluded that these isolated remarks in the literature, which are indicative of some hereditary pattern, testicular dysfunction, and muscular hyperirritability in association with iris atrophy, are certainly not numerous enough to establish any significant relationship between essential iris atrophy and myotonia atrophica. However, these same remarks lead to the belief that this relationship might have been discovered if thorough clinical and laboratory workup had been performed with such discovery in mind.

As far as the two cases reported in this communication are concerned, the idiopathic aspermia and hypogonadism in Case 1, and sterility in Case 2 should be given careful consideration.

It is true that hypogonadism is a part of the complicated syndrome of myotonia atrophica but it should be emphasized that a case cannot be called myotonia atrophica simply because of the presence of hypogonadism. It can be argued, however, that myontonia atrophica can be seen as an incomplete syndrome, and this hypogonadism may represent such an entity.

There is still the argument that follow-up of these cases may later show muscle disturbances. An attempt will be made to check periodically on these two patients for any evidence of muscular involvement.

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# DISCRETE CARCINOMATOUS METASTASES IN THE EXTRINSIC OCULAR MUSCLES*

## A CASE OF CARCINOMA OF THE BREAST WITH EXOPHTHALMIC OPHTHALMOPLEGIA

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This case of exophthalmic ophthalmoplegia, due to intraorbital metastases from mammary cancer, is reported because of the extreme rarity of discrete carcinomatous metastases in the extrinsic eye muscles.

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### CASE HISTORY

Mrs. C. M., aged 72 years, had a painless swelling in her right breast for 12 months which had slowly increased in size. She had obstinately refused medical attention until nausea and vomiting of sudden onset and increasing severity led to her admission to hospital with subacute intestinal obstruction. She volunteered no symptoms other than nausea, vomiting, and profound weakness for three days, but on direct questioning admitted to "a little difficulty in moving her eyes" for several weeks. She denied

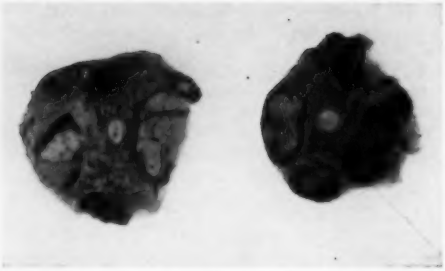

Fig. 1 (Bedford and Daniel). Section across the muscle cones, showing carcinomatous deposits within the extrinsic ocular muscles.

all other ocular symptoms but her relatives stated that her eyes began to bulge about two months previously.

She was very ill but mentally alert and was much troubled by nausea and frequent retching. An indurated mass replaced the whole of the right breast but had not ulcerated through the skin. Secondary deposits of carcinoma were widespread in the liver, the abdominal cavity, the lymph nodes and the skin. The thyroid gland was palpable but not enlarged and although it was slightly nodular, there was no evidence of thyrotoxicosis or myxedema.

She had bilateral exophthalmos, the proptosis being more marked on the left than the right. There was virtually complete external ophthalmoplegia, but the ocular axes were parallel and there was no diplopia. Unaided vision in both eyes was normal. The ocular fundi were normal and the visual fields full to confrontation. The pupils were slightly irregular in outline but were equal in size and reacted briskly to light. There was no chemosis and no puffiness of the eyelids. Detailed examination of the nervous system revealed no other abnormality.

Surgery was considered inadvisable. She became mentally confused, suffered a pathologic fracture of the left hip and died in extreme cachexia 12 days after her admission to hospital.

The assumption that the ophthalmoplegia and exophthalmos were due to invasion of the external ocular muscles by metastases from the cancer of the right breast was confirmed at necropsy.

## Necropsy

There was a moderate sized scirrhous carcinoma of the right breast. Metastases were found in the uterus, ovaries, peritoneum, lymph nodes, skin and several bones, including the left femur, which had a pathologic fracture of its neck. Examination of the fixed brain showed that there were secondary deposits both in the leptomeninges and in the substance of the brain and cerebellum. No secondary deposits were found in the brainstem. Dissection of the eyes and their muscle cones, which had been removed and fixed en bloc, showed that the extrinsic eye muscles were enlarged by tumor (fig. 1). There was no tumor tissue in the orbit except that actually in the eye muscles themselves (fig. 2). Histologic examination showed that the primary tumor of the breast (and the secondary deposits) were composed of spheroidal, anaplastic-looking carcinoma cells. In the orbit the tumor tissue was confined to the extrinsic eye muscles and was not present in any other orbital tissue.

## Comment

Carcinomatous metastases are very rarely found in muscle.[1,2] Duke-Elder[3] points out that "the orbit is a rare site for metastatic carcinomatous deposits," a statement with which all would agree. But his next assertion that "the site of election (for such deposits) is in one or other of the orbital muscles," cannot, we feel, be accepted; certainly it can not be supported by a critical study of the cases in the literature. Similarly Combaud's[4] statement that "the muscles of the eyes are, amongst the tissues of the orbit, those which are undoubtedly the most often infiltrated (by metastatic carcinoma)," is not supported by any evidence, and cannot be substantiated by a study of the recorded cases. Most of the reports of the very rare cases of metastatic cancer of the orbit in which the eye muscles are involved, are of orbital metastases involving the ocular muscles and other orbital tissues and are not examples of discrete metastatic deposits primarily within the muscles themselves. We have found reports of only two cases of discrete secondaries actually within the extrinsic ocular muscles, and one of these is doubtful.

Horner[5] recorded the case of a man, aged 65 years, who had partial ptosis of the upper eyelid and paralysis of all the recti oculi on the right side. He had a hard knobbly goiter and two nodules in the submaxillary region with two more in the abdominal wall. At

necropsy, tumor tissue was found in the dura. The right optic nerve was found to be surrounded at the optic foramen by reddish growth which was continuous with similar tissue which filled one side of the middle cerebral fossa. There were many nodules of tumor elsewhere in the body, including a lump the size of an apple in the pleural cavity and a nodule in the suprarenal. He says that the levator palpebrae superioris and the superior rectus contained nodules of tumor and that the medial, inferior and lateral recti contained nodules in their centers. No histologic examination was made, and we may doubt the correctness of Horner's view that the dural tumor was the primary, and may guess that the primary was in the lung. Nevertheless, this seems to be an unequivocal case of discrete secondary deposits in the eye muscles.

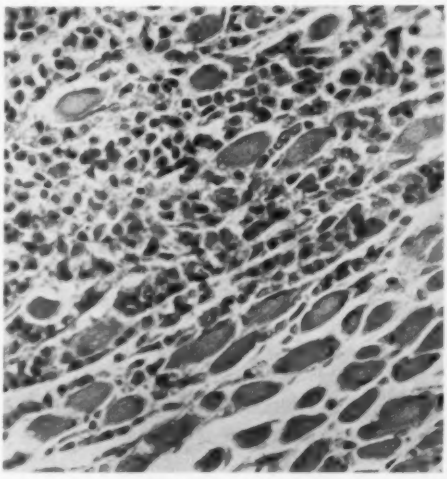

Fig. 2 (Bedford and Daniel). Muscle fibers of extrinsic ocular muscle infiltrated with carcinoma cells.

The only other case that we have been able to find in the literature with apparently similar discrete secondary deposits in the eye muscles is that reported, very sketchily, by Wintersteiner[6] of a woman, aged 58 years, with cancer of the breast who had limitation of movement of the right eye. Post-mortem examination showed a little mass the size of a hemp seed in the middle of the belly of the medial rectus oculi muscle and a nodule in the inferior rectus. He comments that a moderate degree of infiltration need not affect the function of the muscle. Although this case is apparently a "true bill" the report is too sketchy to be acceptable without reserve.

The idea that the extrinsic eye muscles are the site of election for metastatic carcinomatous deposits seems to be derived from the writings of Combaud,[4] Lavaux,[7] and Michail.[8] The two former reviewed the literature on intraorbital metastases, without adding cases of their own and they misinterpreted or misquoted the findings of earlier authors.

Michail[8] also reviewed the literature, adding a case of his own in which the secondary deposits did not involve the muscles and concluded, from a misreading of the literature, that the ocular muscles are the commonest site for secondary deposits in the orbit. He quotes Horner[5] and Wintersteiner[6] and also Elschnig,[9] Axenfeld[10] and Magnus,[11] but perusal of the papers of these latter three authors makes it clear that the site of the original metastatic deposits which they found within the orbit was quite uncertain, and that they certainly were not discrete metastases within individual orbital muscles.

Sniderman[12] repeats the statement that the extrinsic ocular muscles constitute the site of election for metastatic carcinomatous deposits in the orbit, quoting the older authors already mentioned and also reporting two cases of his own with secondary deposits in the orbital muscles from prostatic carcinomas. Other orbital tissues were also involved, however, so that these cases are not acceptable as examples with discrete secondary deposits in the muscles.

We have been unable to find another case in the literature in which secondary deposits occurred as isolated, discrete nodules within the extrinsic ocular muscles. In all the reported cases the interstitial tissues were in-

volved as well as muscle in a mass or masses of growth within the orbit, and no evidence has been adduced as to the site of the original deposition, whether first in the muscle with subsequent invasion of the interstitial tissues, or vice versa, as seems more likely.

SUMMARY

Discrete carcinomatous metastases in the extrinsic muscles of the eyes were found in a woman with cancer of the breast and exophthalmic ophthalmoplegia.

Involvement of the extrinsic ocular muscles by discrete secondary deposits of carcinoma would appear to be exceedingly rare, for the present case is only the third recorded.

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## A NEW SOLUTION FOR TOPICAL APPLICATION IN EXTERNAL EYE INFECTIONS*

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*New York*

The preparation† used in this investigation is a new solution for topical application in infections of the external eye. It contains the two antibiotics, neomycin sulfate (3.5 mg. base/ml. and polymyxin-B sulfate (16,250 units/ml. and, in addition, the antibacterial activity of benzalkonium chloride (0.004 percent) and the vasoconstrictor effect of phenylephrine hydrochloride (0.12 percent). These ingredients are combined in a buffered, isotonic solution containing methylcellulose 4,000 cps. (0.5 percent).

There are several reports in the literature on the activity of the two antibiotics[1-4] and a report has been made concerning the specific concentrations used in this solution.[5]

In order to diminish patient discomfort associated with conjunctival injection, phenylephrine hydrochloride has been added to the solution for its vasoconstrictor activity.

This report describes the results obtained from the topical use of this preparation in 35 unselected cases. Each case was evaluated clinically and individual results recorded. Of

* From the Research Department of the New York Eye and Ear Infirmary.
† Alcon Laboratories, Inc., Fort Worth, Texas, kindly supplied the preparation (Isopto-PNP) used in this study.

TABLE 1

USE OF SOLUTION IN 35 UNSELECTED CASES

| Case No. | Patient | Diagnosis | Therapy | Results |
|---|---|---|---|---|
| 1 | R. L. | Recurrent catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 8 da.—response excellent |
| 2 | H. F. | Blepharoconjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 4 da.—response good |
| 3 | S. F. | Acute catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 3 da.—response excellent |
| 4 | D. Z. | Chemical conjunctivitis, O.S. | gtts ii O.U. q2h | Condition cleared in 3 da.—response excellent |
| 5 | G. T. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 7 da.—response excellent |
| 6 | G. D. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 6 da.—response poor |
| 7 | J. P. | Marginal corneal ulcer, O.D. | gtts ii O.D. q2h | Condition cleared in 3 da.—response excellent |
| 8 | H. P. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 8 da.—response excellent |
| 9 | M. M. | Blepharoconjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 8 da.—response excellent |
| 10 | L. C. | Acute meibomitis left upper lid | gtts ii O.S. q2h | Condition cleared in 6 da.—response excellent |
| 11 | O. F. | Catarrhal conjunctivitis, O.U. | gtts ii O.D. q2h | Condition cleared in 8 da.—response excellent |
| 12 | E. B. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 9 da.—response excellent |
| 13 | H. C. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 3 da.—response excellent |
| 14 | G. K. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 5 da.—response excellent |
| 15 | C. G. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 6 da.—response excellent |
| 16 | J. D. | Acute purulent conjunctivitis, O.S. | gtts ii O.S. q2h | Condition cleared in 8 da.—response excellent |
| 17 | J. K. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 7 da.—response excellent |
| 18 | C. P. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 7 da.—response excellent |
| 19 | G. K. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 5 da.—response excellent |
| 20 | P. P. | Acute purulent keratoconjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 5 da.—response excellent |
| 21 | F.C. | Blepharoconjunctivitis, O.D. | gtts ii O.U. q2h | Condition cleared in 11 da.—response excellent |
| 22 | I. W. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 9 da.—response excellent |

TABLE 1—(*Continued*)

| Case No. | Patient | Diagnosis | Therapy | Results |
|---|---|---|---|---|
| 23 | A. S. | Chronic catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 6 da.—response good |
| 24 | L. G. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 5 da.—response excellent |
| 25 | M. U. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 6 da.—response excellent |
| 26 | G. D. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 5 da.—response excellent |
| 27 | I. G. | Catarrhal conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 6 da.—response excellent |
| 28 | A. D. | Chronic catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 5 da.—response excellent |
| 29 | M. D. | Acute purulent conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 6 da.—response excellent |
| 30 | M. F. | Acute purulent conjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 8 da.—response excellent |
| 31 | Y. C. C. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 8 da.—response excellent |
| 32 | E. G. | Keratoconjunctivitis, O.D. | gtts ii O.D. q2h | Condition cleared in 10 da.—response excellent |
| 33 | H. S. | Catarrhal conjunctivitis, O.U. | gtts ii O.U. q2h | Condition cleared in 7 da.—response excellent |
| 34 | O. S. | Acute purulent conjunctivitis, O.S. | gtts ii O.S. q2h | Condition cleared in 6 da.—response excellent |
| 35 | A. P. | Blepharoconjunctivitis, O.D., associated with acute chalazion right upper lid | gtts ii O.D. q2h | Blepharoconjunctivitis cleared in 9 da.—response excellent, chalazion markedly decreased—response good |

the total, only one patient reported a mild and momentary stinging; no other side-effects were noted. The findings are recorded in Table 1.

Shown on the accompanying pages are five series of color photographs* demonstrating "before" and "after" conditions for Cases 31, 32, 33, 34, and 35.

## Results

Of the 35 cases treated, all showed a recovery varying from three to 11 days, with the majority requiring five to eight days. In Case 6, the response was poor, with keratoconjunctivitis of viral etiology developing. In the one case in which irritative signs appeared on the eighth day, a history of this case disclosed that in previous episodes using other medications, irritative signs commenced as early as the fourth day of treatment.

## Summary

A new topical solution for use in ophthalmology has been tested, and the results obtained are herein reported. The only side-effect noted was mild and momentary stinging in one instance on the eighth day of treatment. The remaining 34 patients showed no signs of irritation or other side-effects.

* Photographs by John P. Goeller, photographer, New York Eye and Ear Infirmary.

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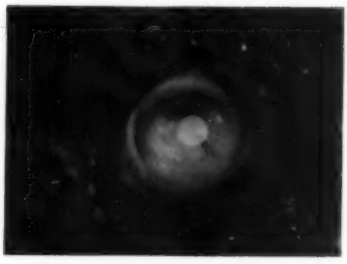

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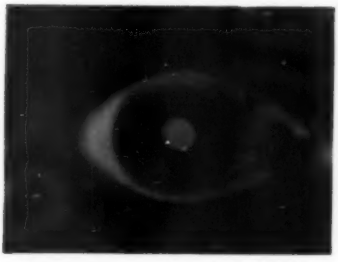

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Figs. 1-6 (Goldberg, Zavell and Kara). A new solution for topical application in external eye infections.

Fig. 1 (before treatment). Case 31. Y. C. C., aged 59 years, a Chinese man with redness and mucoid discharge in both eyes for seven days. Therapy: polymyxin-neomycin-phenylephrine ophthalmic solution, two drops, O.U., every two hours. Organism: hemolytic Staphylococcus aureus, mannitol negative, coagulase negative. Diagnosis: acute catarrhal conjunctivitis. Response: excellent.

Fig. 2 (after treatment). Case 31. Clearing of inflammatory signs within eight days.

Fig. 3 (before treatment). Case 32. E. G., aged 67 years, a white man with recurrent redness and light sensitivity of the right eye.

Fig. 4 (before treatment). Case 32. Diffuse fluorescein staining of central cornea. Therapy: polymyxin-neomycin-phenylephrine ophthalmic solution, two drops, O.D., every two hours. Organism: hemolytic Staphylococcus aureus, coagulase negative, mannitol negative. Diagnosis: keratoconjunctivitis, O.D. Response: excellent.

Fig. 5 (after treatment). Case 32. Complete clearing of corneal staining and conjunctival injection within 10 days.

Fig. 6 (after treatment). Case 32. No fluorescein staining of central cornea.

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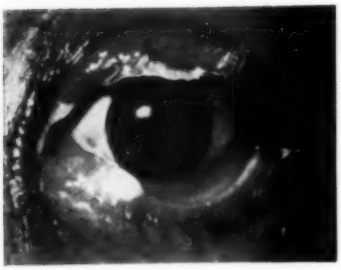

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Figs. 7-14 (Goldberg, Zavell and Kara). A new solution for topical application in external eye infections.

Fig. 7 (before treatment). Case 33. H. S., aged 69 years, a white man with redness and occasional discharge, O.U., of two months' duration. Therapy: polymyxin-neomycin-phenylephrine ophthalmic solution, two drops, O.U., every two hours. Diagnosis: subacute blepharoconjunctivitis. Response: excellent.

Fig. 8 (after treatment). Case 33. Rapid clearing of discharge and redness of palpebral conjunctivas and lid margins.

Figs. 9 and 10 (before treatment). Case 34. A Negress, aged 41 years, with a three-day history of yellowish discharge and painful swelling of the lower lid, O.S. Therapy: polymyxin-neomycin-phenylephrine ophthalmic solution: two drops, O.S., every two hours. Diagnosis: acute purulent conjunctivitis associated with hordeolum of the lower lid, O.S. Response: excellent.

Figs. 11 and 12 (after treatment). Case 34. Complete and rapid clearing of signs and symptoms within six days.

Fig. 13 (before treatment). Case 35. A. P., aged 60 years, a white man with painful swelling of the upper lid, O.D., associated with redness and discharge of seven days' duration. Therapy: polymyxin-neomycin-phenylephrine ophthalmic solution, two drops, O.D., every two hours. Organism: hemolytic Staphylococcus aureus, mannitol positive, coagulase positive. Diagnosis: blepharoconjunctivitis, O.D., associated with acute chalazion upper lid, O.D. Response: blepharoconjunctivitis excellent: chalazion, good.

Fig. 14 (after treatment). Case 35. Discharge, redness and swelling of lid cleared within nine days, with marked decrease in size of chalazion.

The preparation appears to be safe for use and because of its wide antibacterial spectrum, vasoconstrictor and emollient action should prove to be efficacious in treatment and devoid of discomfort to the patient.

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## LONG-TERM PRESERVATION OF DONOR TISSUES FOR CORNEAL GRAFTING*

### CORRELATION OF RESULTS FROM TISSUE CULTURES WITH THOSE FROM EXPERIMENTAL GRAFTINGS


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In order to devise a method for long-term preservation of corneal tissue which results in clear successful grafts, the following two basic questions must be answered: (a) Is it necessary that the donor tissue be in viable condition; or, (b) is it only necessary that the physical structure of the graft be preserved although the tissue may not be viable.

Payrau[1] has obtained clear lamellar grafts using nonviable corneas preserved by lyophilization. King[2] and others also have obtained clear lamellar grafts in animals and humans with corneal tissues preserved by vacuum dehydration even though growth has not been observed in tissue culture experiments with these specimens.[3] Thus, for successful lamellar grafts, viability of donor tissue does not appear to be requisite.

The problem has not been solved as yet where full-thickness or perforating grafts are concerned. King[2] reported that full-thickness corneal grafts in animals with vacuum dehydrated tissue were not successful. The few attempts to use this type of tissue for perforating grafts in humans (King, Castroviejo, Joaquin Barraquer[4]) did not result in clear grafts, that is, either the graft became sclerosed or, if the anterior part of the corneal stroma remained transparent, a dense membrane formed in the area of Descemet's membrane. Payrau,[1] who tried perforating grafts with lyophilized corneas in 10 dogs, 12 rabbits, and two humans, reported a transparent graft in one dog and in one rabbit. The two attempts in humans were failures inasmuch as a dense membrane had formed on or behind Descemet's membrane. Payrau claims that technical difficulties might have been partly responsible for these poor results.

The results with perforating grafts in humans, when dead corneal tissue is used, are indeed discouraging. We therefore decided that it was worthwhile to pursue our hypothesis that a viable and functioning endothelium of the graft might be important for obtaining clear grafts. We have previ-


* From the Duke University School of Medicine, Department of Surgery, Plastic Surgery Research Laboratory, and Division of Ophthalmology. This work was aided by U.S. Public Health Grant B-1161. This work was also aided by Grant No. TR65, Playtex Park Research Institute. Read at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959.


† Fight for Sight research fellow of the National Council to Combat Blindness, Inc., New York.

ously reported a workable method to examine the viability of the three corneal tissues —epithelium, stroma and endothelium—separately in tissue culture[5] and have tested the effect of various methods of preservation on the viability of these tissues.[5] In the present paper we shall demonstrate to what degree the results of tissue culture can be paralleled by actual grafting experiments in animals, such as cats and rabbits.

## Materials and Methods

### Preservation

Corneas were removed as previously described.[5] The method of preservation by glycerol freezing at either −45°C. or −79°C. was as follows: The screw-capped tubes containing the preservative fluid (glycerol, 20 percent, and Hanks' balanced salt solution without sodium biocarbonate, 80 percent) and the cornea were sealed with adhesive tape and paraffin. After soaking one hour at room temperature, the tubes were placed directly into the freezing units and stored there, that is, no controlled rate of freezing was employed. For the freezing at −45°C. the specimen was placed on a shelf of a mechanical refrigerator with artificial air circulation, while for the freezing at −79°C. the tubes were placed directly in and stored in crushed dry ice. Thus with the −79°C. storage there would be no fluctuations in temperature due to an air space which is present in certain types of dry-ice storage boxes.

For the −45°C. the freezing time was previously determined to be approximately 10 minutes with another five minutes required to reach −45°C. The −79°C. temperature required only five minutes to freeze, another six minutes to reach −79°C. Thus the total time for freezing and equilibration for the −45°C. and −79°C. was 15 minutes and 11 minutes, respectively.*

* These data were kindly made available through the courtesy of Dr. A. P. Rinfret, Linde Company, Division of Union Carbide Corporation, Tonawanda, New York.

The corneas were removed from storage and thawed quickly in warm water. The preservative fluid was removed. Rehydration was done in Hanks' balanced salt solution for all cat corneas and for one third of the rabbit corneas. Pooled normal rabbit serum was used for two thirds of the rabbit corneas. The corneas rehydrated in Hanks' solution were left in this medium for 10 to 15 minutes. When rabbit serum was employed the time of soaking varied between 30 minutes and 30 hours.

### Tissue culture

The technique for growing the three corneal layers, epithelium, stroma, and endothelium separately in tissue culture was as previously described.[5]

### Grafting procedures

One hour before operation the fasting rabbit was given 4.0 mg. Thorazin® per lb. intramuscularly and 20 minutes later 0.3 mg. Antrenyl® per lb. intramuscularly. The operative field was prepared by repeated flushing with aqueous solution of Zephiran® 1/1000. The first dose of sodium pentobarbital, 6.0 mg. per lb. was administered intravenously and the animal placed on its side with the head elevated by a one-inch pad. Two ml. of xylocaine hydrochloride (one percent) with epinephrine (1:100,000) was injected into the eyelids, followed by 0.5 ml. retrobulbarly on four sides of the eyeball. Immediately before draping the animal, 3.0 mg. heparine per lb. was injected intravenously. The animal was draped as a sterile field and the operative procedure commenced. Six 4-0 silk sutures were placed through the edge of the upper eyelid and clamped together with a straight forceps. A marking with a five-mm. trephine about 0.4 mm. deep was made on the cornea. Corneal sutures (6-0 silk Ethicon B-780) were placed as two overlying cross sutures (fig. 1).

After the preserved cornea had been thawed and rehydrated the graft was ex-

cised as follows: The cornea was placed with the endothelium superiorly on a paraffin block in which a depression having the curvature of the cornea had been made, the graft being cut with the same five-mm. trephine and transferred to a watch glass containing Hanks' balanced salt solution or rabbit serum. At this time, an additional dose of 3.0 mg. sodium pentobarbital and 0.4 mg. heparin per lb. was injected intravenously. As rabbit serum quickly neutralizes heparin, the drug had to be given at least twice during the operation. If necessary more local anesthesia was injected retrobulbarly at this time. The formation of fibrin in the aqueous during the operation, a disturbing peculiarity especially in the rabbit, was effectively prevented by the administration of heparin intravenously and sodium citrate locally.

With a five-mm. trephine the host cornea was perforated and the excision of the corneal disc was completed with curved corneal scissors. As soon as the anterior chamber was opened a one-percent solution of sodium citrate in saline was dropped continuously on the eye to prevent fibrin formation.

Since a small (five mm.) graft was used the operation was performed with the pupil in mydriasis in order to avoid anterior synechias. If the pupil was not mydriatic 10-percent Neosynephrine® ophthalmic solution was dropped into the anterior chamber. The donor graft was placed into the opening of the host's cornea and the corneal sutures tied. Through a blunt needle an air bubble was injected into the anterior chamber. After instilling atropine and Neosporin® ointment into the conjunctival sac, the eyelids were sutured together, using the silk sutures already present in the upper eyelid. If there was considerable bleeding, an intravenous injection of protamine was given in about the same dosage as the previously injected quantity of heparin. The eyelids were kept closed for three to five days. Penicillin 150,000 units and streptomycin 0.18 gm. were injected intramuscularly at the end of the operation. During the first postoperative week, penicillin, 100,000 units, and streptomycin, 0.13 gm., were administered daily.

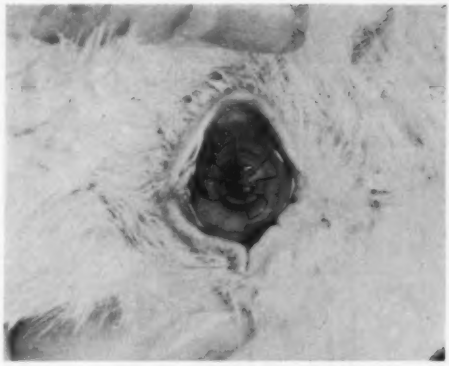

Fig. 1 (Stocker, et al.) Fresh graft in rabbit, showing overlying cross sutures and clear graft in the early postoperative period.

The same procedure was employed for the cats, except no Thorazin® was used and sodium pentobarbital was given intraperitoneally, 15 mg. per lb. one hour before the operation. No heparin was given intravenously.

Fifty experimental grafting operations were performed in cats and 54 in rabbits. Fresh autografts and homografts, fresh and preserved, were used throughout. No heterografts were done.

## Results

### Tissue cultures

In a previous report on results of tissue cultures with rabbit corneas preserved at −45°C. positive cultures of all three layers had been obtained from material frozen for as long as 19 weeks.[6] Since then growth was observed from all three layers of rabbit corneas which had been frozen at −45°C. for 22 weeks.

In order to determine if there was a difference related to species, tissue culture experiments were set up with cat corneas.

When fresh cat corneas were employed, positive cultures from all three layers were obtained. In contrast, growth was very diffi-

TABLE 1

RESULTS OF TISSUE CULTURES FROM CAT CORNEAS FROZEN AT −79°C. OR −45°C.

| Length of Storage | −79°C. | | | −45°C. | | |
|---|---|---|---|---|---|---|
| | Ep | S | En | Ep | S | En |
| 24 hr. | ++ | 0 | 0 | + | + | + |
| 2 wk. | + | + | 0 | + | ++ | 0 |
| 4 wk. | 0 | + | 0 | 0 | 0 | 0 |
| 10 wk. | 0 | 0 | 0 | 0 | + | 0 |
| 11 wk. | 0 | 0 | 0 | + | 0 | 0 |
| 13 wk. | − | − | − | 0 | 0 | 0 |
| 14 wk. | − | − | − | + | + | 0 |
| 15 wk. | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 wk. | 0 | 0 | 0 | + | + | 0 |

++—All cultures positive.
+—Half or more of the cultures positive.
0—No growth.
−—No cultures set-up.
Ep—Epithelium.
S—Stroma.
En—Endothelium.

cult to obtain from frozen cat corneas, as can be seen from Table 1.

From the corneas frozen at −79°C. positive cultures were obtained only from epithelium and stroma. All cultures of the endothelial layer were negative. Furthermore no positive cultures were obtained after four weeks of storage. The results from corneas frozen at −45°C. were more favorable. Positive cultures were obtained from epithelium and stroma when frozen for as long as 16 weeks. The results, however, were irregular. Endothelium was grown from one cornea which had been stored for only 24 hours. All subsequent endothelial cultures were negative.

TABLE 2

RESULTS OF FRESH AND FROZEN CORNEAL GRAFTS IN CATS

| Type Donor Tissue | Number of Cases | Late Results 8 weeks–6 months | |
|---|---|---|---|
| | | Success | Failure |
| Fresh | 25 | 15 | 10 |
| −45°C. | 9 | 1 | 8 |
| −79°C. | 8 | 0 | 8 |
| Total | 42 | 16 | 26 |

### CORNEAL GRAFTS IN CATS

Fifty perforating corneal grafts were performed in cats. Of these 30 were fresh grafts and 20 were frozen at −45°C. and −79°C. for periods of one day to 12 weeks. Unfortunately an infectious disease affected the animals during the early postoperative stage and killed several of them. The results are summarized in Table 2 and include only the 42 operations performed on those animals which survived longer than eight weeks postoperatively. The operation was termed a success if the transparency of the graft was such that it would be termed satisfactory in a clinical case. In the final results 15 of the 25 fresh grafts were successful whereas only one of 17 frozen corneas was considered a success.

### CORNEAL GRAFTS IN RABBITS

Fifty-four corneal grafts were performed in rabbits. Of these, 11 were fresh and 43 were frozen grafts. Twenty-nine of the 43

TABLE 3

RESULTS IN RABBITS OF CORNEAL GRAFTS FROZEN AT −°45C. IN RELATION TO THE LENGTH OF STORAGE TIME

| Freezing Time | Number of Cases | Early Edema 3–5 Days Postoperative | | Number of Cases Left | Middle Period 2–4 Weeks | | | Number of Cases Left | Late Results 6–14 Weeks | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mild | Severe | | Cl.* | Trl. | Op. | | Success | Failure |
| 4 da. | | | | | | | | | | |
| 2 wk. | 7 | 6 | 1 | 5 | 5 | 0 | 0 | 5 | 5 | 0 |
| 2– 7 wk. | 15 | 10 | 5 | 14 | 1 | 8 | 5 | 8 | 3 | 5 |
| 8–13 wk. | 7 | 5 | 2 | 5 | 0 | 0 | 5 | 4 | 1 | 3 |
| Total | 29 | 21 | 8 | 24 | 6 | 8 | 10 | 17 | 9 | 8 |

* Cl.—Clear, Trl.—Translucent, Op.—Opaque.

TABLE 4

RESULTS IN RABBITS OF CORNEAL GRAFTS FROZEN AT −79°C. IN RELATION TO THE LENGTH OF STORAGE TIME

| Freezing Time | Number of Cases | Early Edema 3–5 Days Postoperative | | Number of Cases Left | Middle Period 2–4 Weeks | | | Number of Cases Left | Late Results 6–14 Weeks | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mild | Severe | | Cl.* | Trl. | Op. | | Success | Failure |
| 1– 2 wk. | 5 | 2 | 3 | 5 | 0 | 1 | 4 | 5 | 1 | 4 |
| 2– 5 wk. | 6 | 2 | 4 | 4 | 0 | 0 | 4 | 4 | 1 | 3 |
| 5–21 wk. | 3 | 2 | 1 | 3 | 0 | 1 | 2 | 2 | 0 | 2 |
| Total | 14 | 6 | 8 | 12 | 0 | 2 | 10 | 11 | 2 | 9 |

* Cl.—Clear, Trl.—Translucent, Op.—Opaque.

had been frozen at −45°C., 14 at −79°C. Some of the animals were killed at various stages after the operation in order to get histologic specimens, and nine had to be killed because of infection or injury to the operated eye. Consequently, 17 cases of the −45°C. series and 11 of the −79°C. were left for evaluation of late results. In Tables 3 and 4, the results are summarized according to the length of time the grafts had been frozen at −45°C. and −79°C. respectively. The over-all results are tabulated in Table 5.

For the interpretation of the symptoms during the various phases of the evolution of corneal grafts, it was necessary to distinguish at least three periods:

1. Early period of three to five days postoperative.
2. Middle period of two to four weeks.
3. Late results from six to 14 weeks.

As seen in Table 3, there seems to be a relationship between the length of time during which the grafts had been frozen and the number of clear grafts. The longer the period of storage, the fewer successful grafts were obtained. This trend, however, is not an absolute one. One clear graft was obtained from a cornea which had been frozen at −45°C. for 10 weeks.

As seen in Table 4, the storage temperature of −79°C. resulted in more failures than successes, with no successful grafts resulting from tissue stored longer than five weeks.

Table 5 presents the over-all results from comparing fresh −45°C. and −79°C. donor tissues. In the early postoperative period, the percentage of clear grafts (mild or no edema) was the same whether fresh or corneas preserved at −45°C. were used, that is, 73 percent and 72 percent respectively. When a storage temperature of −79°C. was employed, the incidence of

TABLE 5

RESULTS OF 54 FRESH OR FROZEN CORNEAL GRAFTS IN RABBITS

| Type Donor Tissue | Early Edema 3–5 Days Postoperative | | Middle Period 2–4 Weeks | | | Late Results 6–14 Weeks | |
|---|---|---|---|---|---|---|---|
| | Mild % | Severe % | Cl.* % | Trl. % | Op. % | Scccess % | Failure % |
| Fresh | 73 | 27 | 55 | 18 | 27 | 73 | 27 |
| −45°C. | 72 | 28 | 25 | 33 | 42 | 53 | 47 |
| −79°C. | 43 | 57 | 0 | 17 | 83 | 18 | 82 |

* Cl.—Clear, Trl.—Translucent, Op.—Opaque.

It was found for the late results that statistically there was a significant difference between results of −45°C. and −79°C. Also significant was the difference between fresh and −79°C. In the two transitory periods the figures may be regarded only as an illustration without claiming statistical significance.

Fig. 2 (Stocker, et al.). Frozen graft in rabbit —45°C. No edema in early postoperative period.

clear corneas was reduced to 43 percent (figs. 1, 2, and 3).

During the middle period, 55 percent of the fresh grafts, 25 percent of the grafts frozen at −45°C. and none of the grafts frozen at −79°C. remained clear. Of the latter group, 83 percent showed definite opacification. It was noted that the cloudiness during this period was rarely due to edema and swelling of the whole graft but to an irregular and hypertrophic epithelium. Figure 4 shows the hypertrophic epithelium immediately after removal of the sutures. Figure 5 the same animal five days later. Figure 6 shows how this layer could be lifted with a forceps and how the graft, when relieved of this tissue, usually appeared much clearer. Figures 7 and 8 demonstrate this condition and illustrate how the graft becomes clearer after the epithelial layer is gradually shed and replaced by the host's epithelium. Figure 9 shows the condition in a histologic specimen.

In the late results, up to 14 weeks after the grafting operation, 73 percent of the fresh and 53 percent of the grafts frozen at −45°C. were successful as compared with 18 percent in the group frozen at −79°C. Figures 10, 11, 12, 13, and 14 illustrate failures and successes.

## Discussion

These experiments were designed to determine the correlation between the behavior of fresh and preserved corneal tissue in tissue cultures and in experimental grafting procedures. Corneas from cats and rabbits were employed in an effort to determine if a species difference exists.

The results of the tissue culture experiments with cat corneas demonstrated that cat corneas were very adversly affected by the preservation and storage procedures even for intervals as short as 24 hours (table 1). The endothelium appeared to be most affected as positive endothelial cultures were obtained from tissues stored only for 24 hours at −45°C., while no growth was observed from endothelial cultures of corneas stored at −79°C. Positive cultures were obtained from epithelial and stromal tissues

Fig. 3 (Stocker, et al.). Frozen graft in rabbit —79°C. No edema in early postoperative period.

Fig. 4 (Stocker, et al.). Frozen graft in rabbit —45°C. Hypertrophic epithelium immediately after removal of sutures, 16 days postoperatively.

stored at −45C. for periods as long as 16 weeks, whereas positive cultures of the 79°C. storage tissue were obtained from epithelium stored up to two weeks and from stroma stored for four weeks. Thus a storage temperature of −45°C. appears to be more satisfactory as compared with −79°C.

It is generally accepted that corneal grafting operations with fresh material in experimental animals result in about 50 percent clear grafts. In the present experiment most of the failures were caused by the formation of anterior synechias, vascularization, or sloughing of the graft due to trauma inflicted by the animal. As already mentioned such complications have been rather frequent in this series. The results obtained with fresh cat corneas may therefore be considered as above average.

The poor results of tissue cultures from cat corneas frozen at −79°C. or −45°C. correspond with the negative results of the grafting operations. One successful graft was obtained out of 17 operations.

Also in accordance with the results from tissue cultures are the slightly better results with corneas frozen at −45°C. than those at −79°C. In one case a −79°C. graft was done on the right eye, a −45°C. graft in the left eye. As seen from Figure 15 both grafts were originally opaque, the −79°C. more so. Later the −45°C. became progressively clearer, whereas the −79°C. one remained opaque (fig. 16). Thus there appears to be a definite correlation between the tissue culture results and the grafting experiments.

Fig. 5 (Stocker, et al.). Same as Figure 4, three weeks postoperatively.

Fig. 6 (Stocker, et al.). Same as Figures 4 and 5. Hypertrophic epithelium begins to slough. The stroma is much clearer.

In the evolution of the corneal grafts in rabbits, three periods were observed:

The first period may be termed as the time during which the graft still maintains its original properties and is not yet markedly influenced by the reaction of the recipient's tissue.

During the second period, the recipient begins to react to the foreign tissue while

Fig. 7 (Stocker, et al.). Frozen graft in rabbit −79°C. Spontaneous sloughing of hypertrophic epithelium, three weeks postoperatively.

Fig. 8. (Stocker, et al.). Same as Figure 7. Graft begins to clear after the layer of hypertrophic epithelium is shed.

the graft establishes itself as part of the recipient's body.

The third period represents the final result. In the case of corneal grafts, the final criterion of success is the optical quality regardless of the question how much of the graft is actually surviving or to what degree it is replaced by the host's tissue.

A study of the results of frozen grafts according to the length of time the tissue had been stored at −45°C. brought out the interesting fact that the length of storage seemed to have an effect inasmuch as more favorable results were observed with material stored over a short period (table 3).

This "shift to the right," as seen in Table 3 appeared logical. The longer the tissue had been stored in the frozen state, the more it was damaged and reduced in its viability. This parallels the results previously obtained by tissue cultures of the endothelium.[6] The fact that the shift was more pronounced with freezing temperature of −79°C. instead of −45°C. was in agreement with our tissue culture results.

The observation that the number of favorable results of grafting began to drop off after a comparatively short period was at first glance rather discouraging as far as the outlook for long-term preservation was concerned. There was, however, one case of a cornea which had been frozen at −45°C. for 10 weeks and had an interesting clinical course. It was clear at the beginning, became cloudy during the middle period and cleared satisfactorily after 12 weeks. This observation may be interpreted as follows:

Whereas, by and large, the length of storage in the frozen stage seems to have a definite influence on the viability of the tissue, there may be other factors such as rate of freezing and thawing, rehydration media, and so forth, which possibly might

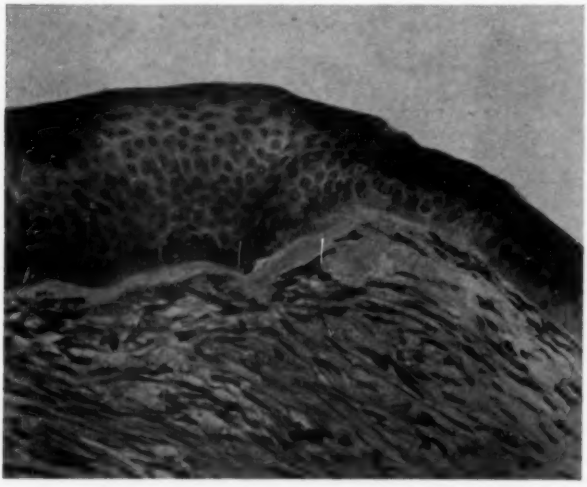

Fig. 9 (Stocker, et al.). Microphotograph of rabbit cornea showing the histology of hypertrophic epithelium described in Figures 4 to 7.

reduce the damage. Further research is necessary to study these factors.

We have observed that the method of rehydration is of great importance. The acute edema which has been observed by other authors during the early stages of the graft may have been in many instances due to excessive rehydration. The following observation has led us to the use of a more physiologic method of rehydration than with the customary salt solutions.

Instead of setting up tissue cultures from frozen rabbit corneas immediately after thawing, tissue was soaked in rabbit serum at −4°C., up to 24 hours. It was observed that the tissues grew much faster and more vigorously than they did without soaking. It was concluded that the serum might have had a revitalizing effect on the tissue and on the endothelium in particular and that soaking in serum instead of salt solutions might provide for a more physiologic rehydration.

After quick thawing the preservative fluid was poured out of the container and replaced by rabbit serum. After two to three minutes the serum was removed and fresh serum added. This was repeated a third time and the cornea left in the serum for a period from 30 minutes to 24 hours.

About 70 percent of our frozen grafts have been rehydrated in this manner, and we believe that this factor is partly responsible for the excellent appearance of the grafts during the initial postoperative period. It is possible that even the final result may be influenced by this method of removing the glycerol and rehydrating the cornea in a physiologic medium such as serum.

Finally, a comparison of the general course of the fresh and frozen grafts (table 5) indicates that, although after a certain length of time satisfactory results may be obtained from corneas frozen and stored at −45°C. and at a much lesser degree from those frozen at −79°C., there is a

Fig. 11 (Stocker, et al.). Frozen graft in rabbit —79°C., seven weeks postoperatively. The graft is completely opaque, failure.

Fig. 10 (Stocker, et al.). Frozen graft in rabbit —45°C., nine weeks postoperatively. The graft is completely sclerosed, failure.

Fig. 12 (Stocker, et al.). Fresh graft in rabbit, 13 weeks postoperatively. The graft is satisfactorily clear, success.

Fig. 13 (Stocker, et al.). Frozen graft in rabbit —45°C., eight weeks postoperatively. The graft is satisfactorily clear, success.

Fig. 14 (Stocker, et al.). Frozen graft in rabbit —79°C., six weeks postoperatively. The graft is satisfactorily clear, success.

considerable difference in the behavior. Most of the fresh grafts which turn out to be successes stay clear, or almost so, right from the beginning. In contrast, the successful frozen grafts may be clear during the first few days, but afterward, most of them go through a period of more or less severe opacification, and they take considerably longer to clear.

It was noted that the cloudiness during this period was rarely due to edema and swelling of the whole graft but to an irregular and hypertrophic epithelium which in many cases was shed and replaced by host epithelium. The real meaning of this peculiar phenomenon is not quite clear. Possibly the frozen epithelium still possessed considerable proliferating power, as demonstrated in tissue cultures, but in the presence of the active epithelium of the host it faces degeneration and death.

The corneal grafting experiments in rabbits demonstrate a direct correlation with tissue culture results[6] in regard to the effect of temperature and length of storage.

Comparing the results of corneal grafts in cats with those in rabbits, it was of par-

Fig. 15 (Stocker, et al.). Frozen grafts in cat 20 weeks postoperatively. The graft in the right eye was frozen at —79°C., the one in the left eye at —45°C. Both grafts are opaque, the one frozen at —79°C., more so. Both eyes were operated on the same day.

Fig. 16 (Stocker, et al.). Same as Figure 15, four weeks later. The graft of the right eye which was frozen at −79°C., remained sclerosed, the one of the left eye which was frozen at −45°C., has cleared considerably.

ticular interest that the results in rabbits were much more favorable than those in cats. Considering the fact that the endothelium of the rabbit cornea does withstand freezing for a long time, whereas the cat's endothelium does not survive, as demonstrated by tissue cultures, these results may constitute another argument in favor of the theory that a viable endothelium is essential for successful penetrating grafts.

The analysis of the effect of the two freezing temperatures, −45°C. and −79°C., on the results of experimental grafts in animals brought out the parallelism between the results of tissue cultures and those of experimental grafts. The temperature of −45°C. was found to be preferable to −79°C. in both instances. By this, it was possible to confirm the in vitro method of our differential technique of tissue culture, growing epithelium, stroma and endothelium separately, as a valid aid in determining the suitability of preserved corneal tissue for penetrating grafts.

From the experiments with animals, it was learned that the tolerance of the corneal tissue to glycerol freezing may vary from species to species, and that caution is necessary in applying animal experiments to humans. For that reason, we now are engaged in extensive studies to evaluate the human cornea, fresh and preserved, by the tissue culture method. Fortunately, it appears from our early observations with human corneas that the results approximate more those obtained in rabbits than those in cats. Because of the many factors involved (time of enucleation after death, time after enucleation cultures are set up, age of patients, and so forth), a great number of corneas will have to be processed before definite conclusions may be reached.

It is felt that preservation of the endothelium in a viable stage is essential for success and that improvements in the technique of freezing, thawing, and rehydration may lead to a long-term storage method. It is possible that improved preserved tissue might even be preferable to fresh tissue. A reduced vitality might eliminate some of the foreign tissue reactions, which are thought to be responsible for some of the clinical failures. Yet, the tissue probably should not be completely dead in the case of perforating grafts. The combination of our method of differential tissue cultures with experimental grafts appears to be a valuable help for making a decision whether clinical use of any type of preserved tissue is justified. As of now we feel that corneal tissue frozen at −45°C. may well be used in emergencies when no fresh tissue is available but it cannot be recommended as yet for long-term banking to substitute fresh tissue routinely.

SUMMARY

1. A comparative study of results from tissue cultures growing epithelium, stroma and endothelium of the cornea separately, with those obtained by experimental corneal graftings in cats and rabbits using fresh and glycerol frozen corneas, reveals that there is considerable agreement between the results of the two methods.

2. The results are better when a freezing temperature of −45°C. rather than −79°C. is used. This is consistent with the theory that a viable endothelium may be important for the success of perforating grafts.

3. Results of experimental graftings with corneas preserved at −45°C. are encouraging. This method of long-term preservation seems to offer the best chances of any method reported so far where perforating grafts are concerned.

4. It is hoped that by further improving the method of freezing, thawing, and rehydrating even better results may be obtained.

5. The combination of tissue cultures and experimental grafts offers a valuable method for evaluating preserved corneal tissue with regard to its clinical use.

6. Corneal tissue preserved by the method of glycerol freezing at −45°C. is not yet recommended for routine human use, substituting fresh tissue, but it may well be used in emergencies, when no fresh tissue is available.

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# IMMUNOCHEMICAL ANALYSIS OF EXPERIMENTAL CORNEAL TRANSPLANTS*

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The following experiments were carried out in an effort to throw some light on the still moot question of whether corneal transplants are replaced by the host tissue or whether they remain essentially unchanged. It was felt that such a study might also help to explain the mechanism giving rise to opacification of corneal transplants in humans at varying intervals of time.

An extensive history of corneal transplantation is not reported here, since it would only be repetitious. Only those investigations having to do with the immediate problem at hand have been quoted.

Salzer (1900) and Bonnefon (1918) sug-

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gested that the corneal transplant is replaced by proliferation of the host tissue into the graft, in which the foreign tissue acts as a framework and undergoes extensive structural changes. Although in Salzer's opinion all grafts are regenerated, he suggested that heterogenous transplants are not promising. The studies of Fuchs (1901), Leoz Ortin (1914), Ascher (1922) and Sommer (1925) on the other hand conclude that the transplants remain unchanged and retain their normal vitality.

Fleischer (1921) reported epithelial degeneration of heterotransplants within 15 days after implantation into the abdominal wall in rabbits, while the epithelium of homotransplants remained unchanged for a period of 35 days.

Choyce (1949), in his paper on nonperforating keratoplasties in rabbits, reported studies carried out on histologic sections and by biomicroscopic observations. He concluded that the epithelium and the substantia propria remained unchanged in their identity over a period of seven months. No signs of replacement of the graft by the host tissue were noticeable, but an eventual replacement by cells from the host in the normal course of events was suggested.

Filatov (1935 and 1945) suggested that a true union of the graft and host tissue takes place and that there is no ingrowth of corneal elements from the recipient. He found, in a graft removed three years after transplantation, that the margin of the graft could be identified and that the arrangement of the lamellae were regular for the entire length of the graft. Remaining cellular infiltration and scar tissue were found only in the area of the junction. The same author described in other publications (1936 and 1937) the influence of transplanted corneal tissue on the surrounding host cornea. He found that absorption of corneal opacity and clearing of the neighboring host cornea occurred.

Similar findings were reported by Chechick-Kunina (1944). The mechanism of clearing was thought to be due to an improvement of the corneal nutrition (Black, 1949). The report of Rexed (1951), who found in histologic studies that Schwannian sheaths survived in the grafts for a period of seven and one-half months, tends to support the theory that the transplanted tissue retained its own characteristics. The fact that devitalized grafts are frequently not successful may be considered as suggestive of the transplant's ability to remain clear only if vitality persists.

Conversely, Salzer (1937) and Scherschewskaya (1940) iterated that the healing of formalized grafts and preservation of their functional capacity must be considered as signs of regeneration.

The regeneration theory is mainly based on the observations reported by Salzer. He believed that the graft is replaced by cells originating from the epithelium and that keratoblasts derived from these cells grow into the transplanted tissue and replace it.

Alphen (1952) demonstrated formation of new tissue similar to that of normal cornea. He implanted a plasma film, without histologic structure, in a perforating trephine hole and observed the development of new tissue structure within the plasma. The new tissue showed transparency with only slight clouding of Descemet's membrane. In contrast to Salzer, he was of the opinion that the host endothelium and Descemet's membrane play an important part in the new tissue formation, while the host epithelium produced only new epithelial cells. Success with heterogenous transplants was explained as being due to a complete replacement of the heterogenous graft by host tissue.

Choyce (1952) used corneal transplants from the human and the cat as grafts in the cornea of rabbits. These transplants were said to be clear, with homogenous fibers and structures similar to the host tissue after a period of two years.

Babel and Bourquin, (1952), reported on successful heterogenous grafts which they implanted by means of an interlamellar tech-

nique into rabbit eyes. They observed that a portion of the transplants stayed clear, while others showed marked anaphylactic reaction with eosinophilic infiltration in both the host tissue and the graft.

The work of Winkelman (1951) and Müller and Maumenee (1952) showed that scleral tissue transplanted into the cornea becomes clear or at least semitransparent. Winkelman thought that the scleral tissue had been replaced by collagenous fibers following necrosis and absorption, but histologic examination did not show any signs of necrotic tissue. Müller and Maumenee explained the semitransparency as being due to scar tissue formation rather than a true clearing of scleral tissue.

The question of whether or not corneal stroma cells can regenerate in destroyed corneal tissue was answered by Maumenee and Kornblueth (1948). It was demonstrated by them that these cells were definitely replaced after previous destruction by freezing variously sized areas of the cornea to −78°C. Beginning replacement in the periphery was observed after 72 hours. In addition, serologic studies in connection with these transplants had been done previously.

In 1911 Löhlein pointed out that a decrease in the antigen action of the transplant may result in a lessening of cloudiness of the graft.

Elschnig (1930) mentioned in an extensive report on corneal transplants, which were done in his clinic, that no relationship was found between hemolysis or agglutination of the serum and the opacification of the corneal graft.

Of major interest, with regard to our present experiments, were the observations of Müller and Maumenee in 1952. These authors set up experiments which attempted to elucidate the problem of corneal clouding in humans, one to six weeks after transplantation. In these studies on animals, it was found that production of a specific hyperergy against the donor tissue resulted in changes similar to those observed in human transplants. This reaction could be increased considerably if additional living tissue of the donor was transplanted into the recipient. An increase took place, however, only if the transplanted tissue was obtained from the same animal as the corneal graft, but not if it came from another animal of the same species.

This experiment demonstrates unequivocally the effect of individual specific hyperergic reaction on the corneal transplants. Because of these findings, the authors suggested that the developed cloudiness, arising from specific hyperergic reaction, may serve as a biologic test demonstrating the survival of host tissue within the recipient. When skin or other tissue was transplanted later than four weeks after corneal transplantation, the effect noted was moot. These observations may be explained by a decrease in reactivity due to loss of antigenic specificity.

Recent reports of Babel and Bourquin (1952) demonstrated that heterogenous transplants became cloudy only if, prior to the transplantation, the host be sensitized against the same animal from which the graft was taken. If, on the other hand, the transplantation was carried out prior to an additional sensitization, no reaction occurred.

Lieb and Lerman (1958) found that interlamellar corneal stroma transplanted to both eyes at different times did not necessarily show an unfavorable response; but a definite reaction was found in the second eye if penetrating grafts had been performed. A similar defense reaction in the second eye took place if frozen corneal stroma was transplanted or when the epithelium of the grafts was left in place. All of these experiments were done with heterogenous corneal material.

Studies made by Dohlman, using $S^{35}$ and $P^{32}$, support the theory that the stromal fibers and Descemet's membrane of a corneal homograft are not replaced, but the interfibrillar ground substance and the cells are

rapidly replaced by the host. It should be mentioned here that these observations were made over a period of 40 days and, therefore, do not give information as to the extent to which the remaining tissue undergoes changes with a further passage of time.

All the previously mentioned observations point to the fact that antigen-antibody reactions play an important part in the outcome of corneal transplantations. The advent of steroid therapy has helped to prevent disappointing results in many instances, but such therapy is still not the complete answer to this problem.

The question of whether or not transplanted corneal tissue will be replaced by host tissue or whether it retains its own characteristics has been approached in most instances by clinical experimentation. The variety of answers obtained is due in a large measure to the great number of unknown biologic factors which can and do occur throughout the observation period. The question of whether the transplant is in truth replaced or merely loses its antigenicity cannot be answered clinically.

Because of the contradictory results noted where clinical experiments have been carried out, we have approached the problem by studying corneal transplants in vitro. Two principal questions were posed:

1. Does the corneal transplant preserve its individual character?

2. During what period of time will the graft be replaced or have lost its antigenicity?

The experimental animals were divided into three main groups: (1) Rabbits with heterogenous corneal grafts, (2) rabbits with homogenous corneal grafts, and (3) rabbits immunized against dog-cornea protein.

In addition to the corneal transplantation and specific immunization of rabbits, two other methods based on antigen-antibody reaction were also employed: (1) Specific precipitation in gels with (a) antigen extract as external reactant and (b) antigenic tissue as external reactant; and (2) turbidimetric measurements.

## Method and Comments

Sixty-six male chincilla rabbits, weighing two to three kg., were used in this experiment. Five additional rabbits were kept as replacements.

### A. Corneal transplantation

In the first part of the experiment, corneal grafts from dog eyes were implanted intralamellarly into the cornea of rabbits by means of the technique described by Maumenee and Bock.

Antibiotic ophthalmic ointment was applied to each of the rabbit eyes 48 and 24 hours prior to transplantation. On the day of transplantation, all rabbits were anesthetized intravenously with sodium nembutal 30 mg./kg. body weight. The area around the eyes was shaved, prepared with tincture of iodine, and draped with sterile sheets. Under aseptic conditions, an incision seven mm. in length was made in the rabbit's cornea at a distance two mm. central to the limbus. The incision extended almost to Descemet's membrane. With a small blunt and slightly curved spatula, the corneal layers were separated to the limbus area opposite the incision, leaving a pocketlike area within the cornea. A corneal graft, measuring 5.5 mm. in diameter and having a thickness of 0.6 mm., was obtained from a freshly enucleated dog eye, from which the epithelial layer had been removed previously. This corneal graft was then implanted into the pocket of the rabbit cornea, and antibiotic ophthalmic ointment was applied. Both eyes of each rabbit were prepared in the same way. The rabbits were closely observed and any changes in the transplant or the whole rabbit cornea were recorded.

Eighteen rabbits with homogenous transplants were used as a control group.

The animals were divided into six groups according to different time intervals.

### B. Procedure for obtaining specific antidog serum

Additional rabbits were immunized, in order to obtain species-specific antibodies against dog-corneal protein. Corneal tissue obtained from dog eyes was homogenized and extracted with sterile 0.8-percent saline solution for a period of 48 hours at 4°C. One ml. of the extract was injected by intramuscular and one ml. by intraperitoneal route every week for four weeks. Full-thickness dog corneas were implanted, subcutaneously, in the abdominal wall of the same animals during the first week.

At the end of five weeks, the rabbit serum was tested for dog-specific antibodies.

*Procedure.* Dog cornea was extracted with 10 times its weight of sterile physiologic saline solution at 4°C. for 24 hours. The extract was then diluted 1 : 1,000, 1 : 10,000 and 1 : 20,000 with sterile physiologic NaCl solution. One cc. of each dilution was put in a separate test tube, and one cc. physiologic NaCl solution was placed in a fourth test tube. To each of the four tubes, 0.1 cc. of centrifuged (5,000 r/min.) specific serum was added. The titer was recorded as the highest dilution giving a definite reaction. The preparation was carried out as recommended by Uhlenhuth. If the titer was found to be high enough, the animals were bled by cardiac puncture, feeding being held in abeyance for the previous 24 hours.

To exclude errors in the exact determination of the titer of this serum, standardized serum obtained from the Pharmaceutical Company "Behringwerke," Marburg —Lahn with precipitin titer of antidog 1: 20,000, 1:10,000 and 1:5,000 was used. While serum I (1:20,000) shows an unspecific quota against cat proteins up to titer 500, serum II and III (1:10,000 and 1: 5,000) are absolutely specific against dog proteins.

In order to determine the presence and the amount of foreign proteins remaining in the graft after a certain length of time, two different methods were used.

### C. Agar-diffusion technique

In the first investigation, an immunochemical analysis was carried out using a modification of the Oudin agar-diffusion technique. This method was originally introduced by Bechhold in 1905.

The experiment was carried out in two different fashions.

1. Agar was first washed in distilled water and then suspended in distilled water to give a concentration of five percent (W/V). The suspension was then dissolved in a boiling water bath and autoclaved at 115°C. for 15 minutes. The sterile solution was clarified by centrifuging, and distilled water was added to obtain a 2.5-percent concentration. Solid NaCl was finally added to give a concentration of 0.85 percent.

Plane tubes, 100 mm. long, of constant five mm. I.D. and five mm. O.D., were used. The tubes were prepared by heating them to 70°C. and filling with 0.8 percent agar solution at the same temperature, so that the agar would stick to the glass wall. The tubes were emptied immediately, placed in an ice bath and then dried in a vacuum desiccator over sulfuric acid for three days.

The agar suspension prepared earlier was melted in a boiling water bath and placed in a bath at 48°C. At this temperature, it was mixed in equal proportions with different dilutions of the antidog serum (internal reactant) at the same temperature. Merthiolate at a concentration of $2 \times 10^{-4}$ gm./100 ml. was added as antiseptic agent. The solution was pipetted into the coated tubes to a level of 50 mm. After the solution had solidified, the corneal area in which the corneal transplant had been imbedded was excised and extracted with 10 times its weight of normal saline solution under refrigeration for 24 hours. This extract was then filtered for complete clarification, and sterile physiologic NaCl solution was added to a final dilu-

tion of 1:500. The degree of dilution was tested in three ways: (a) the foam test; (b) nitric acid test, which gives mild haziness if one drop of nitric acid, specific gravity 1.15, is added to one cc. of the extract; (c) neutral reaction to litmus paper. The corneal extract (external reactant) was then added to a height of 40 mm. The tubes were sealed with wax and kept at a constant temperature of 25°C., resp. 4°C., for seven days. Readings were taken under lateral illumination against a black background.

2. In this method, the same technique of preparing agar tubes was used as described under (1). A piece of the corneal transplant was imbedded at the top of the agar column containing antidog serum. Readings were performed in the same way as described under (1). This method was also used in the following modification. Agar is placed in a petri dish and several holes, about one cm. in diameter and at distances of about 1.5 cm. from each other, are cut out of the solidified gel. The antibody serum is placed in a central hole, and the antigen extract or the antigenic tissue is placed in the peripheral holes. Precipitin reaction will be seen at a temperature of 4°C. after several days.

The reaction obtained within the test tubes depends on two phenomena, diffusion and specific precipitation. Both antigen and antibody diffuse toward each other according to the well-known Fick's Law

$$\left(\frac{dc}{dt}\right)_x = D\left(\frac{d^2c}{dx^2}\right)_t$$

where D is the diffusion coefficient, c the concentration, x the distance in the direction of diffusion and t the time. When antigen and antibody meet, precipitation occurs. All the antigen which diffuses toward the region containing antibody is precipitated. Excess antibody diffusing into the region of antigen remains in solution because specific precipitates are soluble in antigen excess. The end-result is a line of specific precipitate for every antibody-antigen system, the position of which depends on both diffusion coefficient and concentration of the partners.

### D. Control tests

Controls were done in each of the above experiments with pure dog corneas, pure rabbit corneas, corneas with homogenous transplants, as well as with normal NaCl solution.

### E. Turbidimetric method

The area of the corneal graft was removed by using a 5.5 mm. trephine, and the tissue was placed in a sterile test tube in 0.1 cc. normal saline solution.

After 48 hours of extraction at 4°C., the precipitation reaction was performed and quantitated by measuring the light absorption at 600 mμ in a Beckman DU Spectrophotometer equipped with a photomultiplier tube. First 0.08 ml. antiserum was placed into a quartz microcell, which was 10 mm. deep and two mm. wide, and then 0.08 ml. of the corneal extract was added and mixed with the serum immediately. The absorbancy was read at intervals of two minutes initially and then at longer intervals as indicated in the figures. The wavelength of 600 mμ was chosen to minimize the light absorption by the pigments of the antiserum. A 1:1 dilution of antiserum with saline served as baseline.

Control readings were carried out to correct inherent light absorption by the antiserum and antigen solution. The reaction was carried out at a temperature of approximately 28°C. ± 1. Between the 12, 24, and 48-hour readings, the solution was stored in the refrigerator, well sealed with Parafilm to cut to a minimum the number of errors due to contamination or evaporation.

The rate of precipitation may be slightly different in the case of antigen excess as compared with the region of antibody-antigen equivalence or the region of antibody excess. The method of light transmission to determine precipitate formation and its principles is different from those in light-scatter-

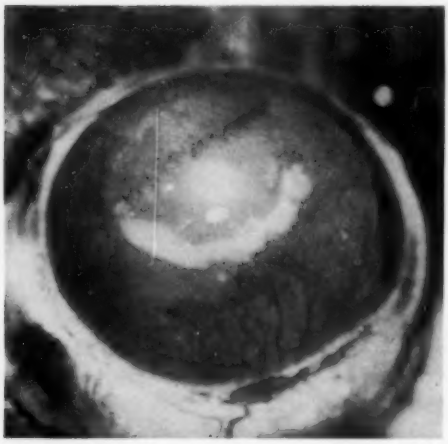

Fig. 1 (Geeraets, Lieb, Chan and Guerry). Vascularization of a heterogenous corneal graft three weeks after transplantation.

ing photoelectric measurements. Gitlin and Edelhoch, using the latter method with a light scattering at an angle of 90 degrees, demonstrated that antigen-antibody combination occurs in a higher velocity on the side of antigen excess. Their observations were done on the precipitin reaction of human serum albumin and its homologous equine antiserum.

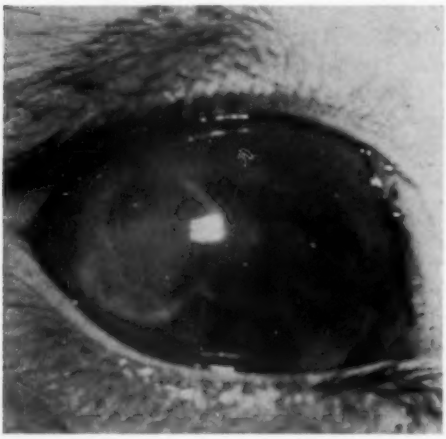

Fig. 2 (Geeraets, Lieb, Chan and Guerry). Heterogenous corneal graft one week after transplantation, showing the graft and surrounding host cornea to be hazy.

With findings similar to theirs, the same early trend in increased combination of antigens and antibodies can be observed with the light transmittance procedure. In antigen excess, the initial rate of precipitate formation may be high, but then the optical density slowly decreases. In antibody excess or antigen-antibody equivalence, increase in optical density continues but at a slow rate.

Caution is necessary in the quantitative interpretation of absorbancies representing light scattering. The proportion of light scattered depends not only on the quantity of suspended particles but also on other factors such as size and shape of the particles and on the wavelength used for measurement. The assumption that increased turbidity indicates increased amounts may be accepted in the present work, since the conditions of the precipitin reaction were kept uniform through-out and since no effects were observed which would seriously interfere with this assumption.

## Results and Discussion

### Clinical observations

All experimental animals, in which heterogenous transplants had been performed, showed, almost without exception, an in-

Fig. 3 (Geeraets, Lieb, Chan and Guerry). Opacity in a heterogenous corneal graft four weeks after transplantation.

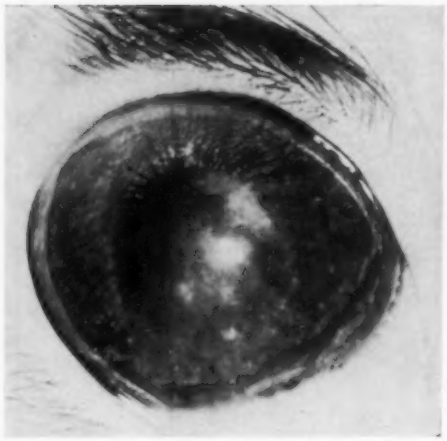

Fig. 4 (Geeraets, Lieb, Chan and Guerry). Same graft as in Figure 3, six months after transplantation. The graft has cleared except for several small opacities.

creased haziness and, finally, opacification of the graft. Such haziness usually started about one week after transplantation and reached its maximum during the third week. At that time, the surrounding host cornea showed similar haziness. In most instances, after four weeks the host cornea cleared but in approximately one third of the animal eyes the graft became more opaque. In some

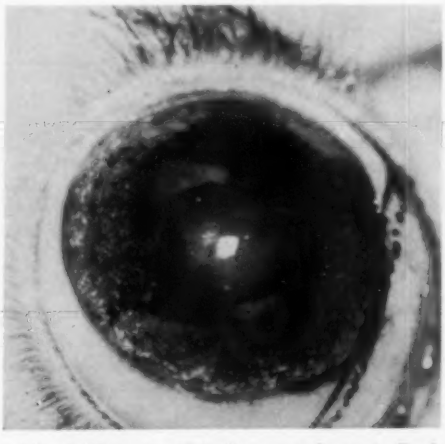

Fig. 5 (Geeraets, Lieb, Chan and Guerry). Graft and surrounding host tissue of Figure 3 after nine months. The entire cornea is completely transparent.

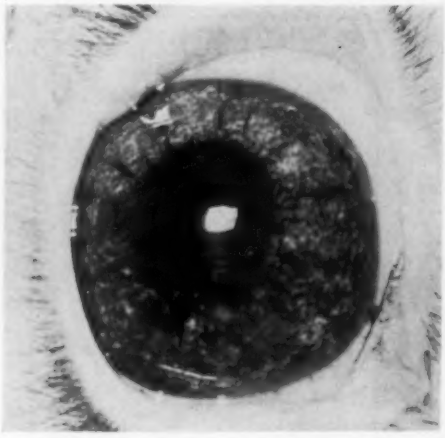

Fig. 6 (Geeraets, Lieb, Chan and Guerry). Graft of Figure 3 after 12 months. The graft almost cannot be recognized any more.

of the animals, ingrowing vessels from the limbus were observed (fig. 1). The opacities persisted for almost six months, but thereafter, in all of the animals which had been kept for further studies, the grafts cleared. In the group of animals kept for nine months, the corneas showed only small areas of scar formation. Grafts and corneas in which the transplant had remained over a

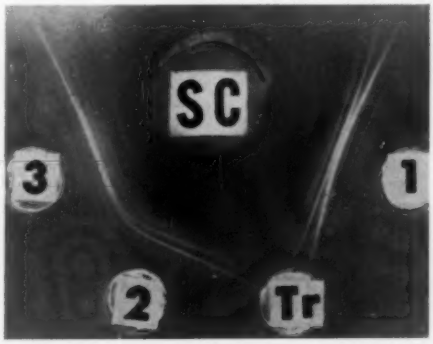


Fig. 7 (Geeraets, Lieb, Chan and Guerry). Precipitin reaction in agar plate. (SC) Rabbit anti-dog-cornea serum. (Tr) Heterogenous (dog) corneal graft which had remained for 10 days in the rabbit cornea: (1) fresh dog corneal tissue (full thickness); (2) dog corneal tissue consisting of Bowman's membrane and stroma; (3) dog cornea consisting of stroma, Descemet's membrane and endothelium.

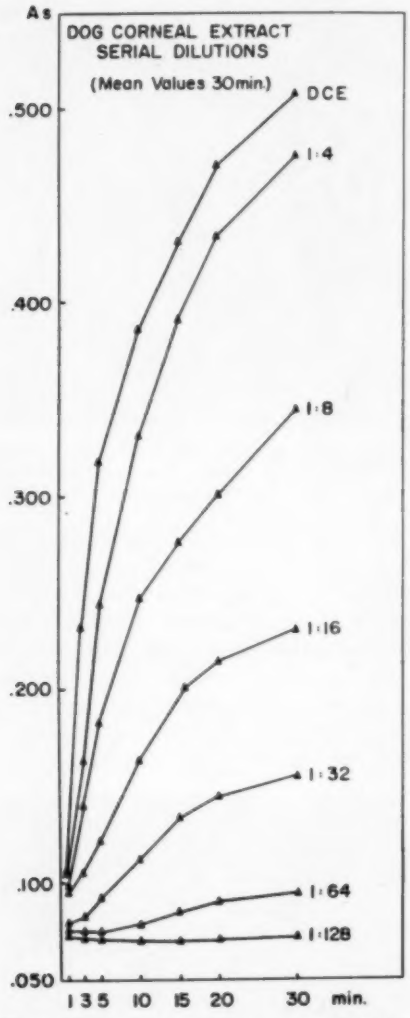


Fig. 8 (Geeraets, Lieb, Chan and Guerry). The different curves are constructed from mean values of turbidimetric readings of precipitin reactions of rabbit-antidog cornea serum with serial dilutions of fresh dog corneal extract. The mean values were obtained from 35 readings for each point. (As) Absorbancy. (DCE) Undiluted corneal extract: the numbers behind the curves give the degree of dilution. Values obtained over a period of 30 minutes.

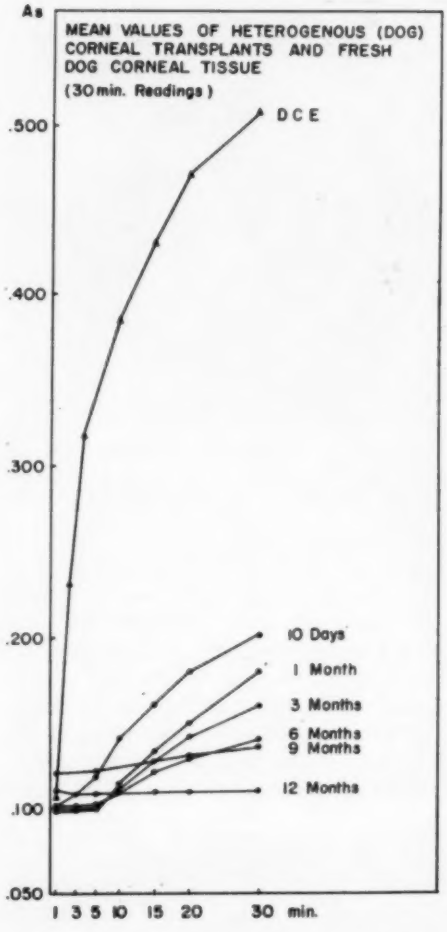


Fig. 9 (Geeraets, Lieb, Chan and Guerry). Mean values of absorbancy (As) obtained from the 30-minute readings of the six main groups of heterogenous (dog) corneal grafts in comparison with fresh dog corneal tissue (DCE). The numbers behind the curves indicate the time over which the transplants had remained in the rabbit cornea.

period of 12 months were completely clear (figs. 2 to 6). The transplant could not even be seen in five eyes out of 14. The observation described above, in which all of the heterogenous transplants became cloudy for a certain period of time, although the epithelium had been previously removed, is not in full agreement with other publications.

Still unanswered is the question of whether corneal epithelium is of higher antigenicity, that is, causes a higher antibody formation than the remaining corneal struc-

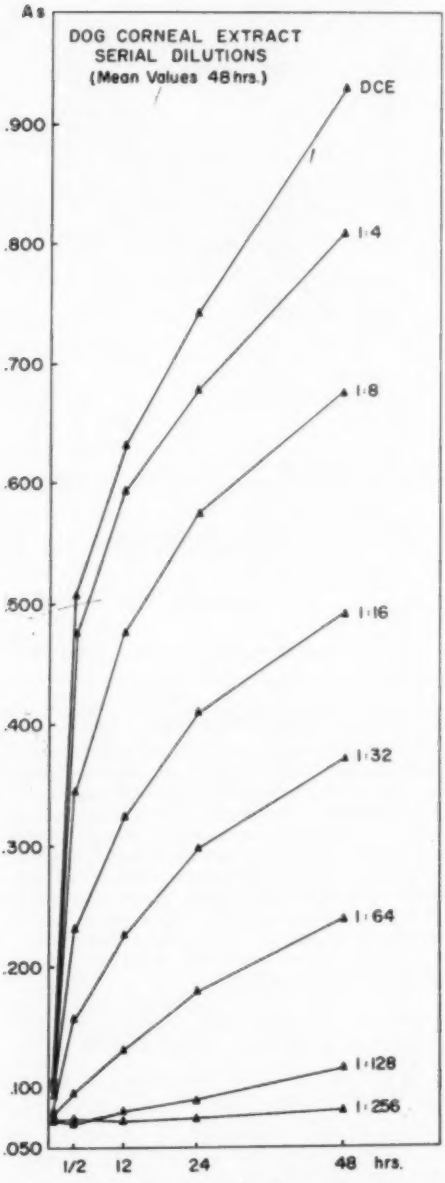


Fig. 10 (Geeraets, Lieb, Chan and Guerry). Mean values of turbidimetric readings with serial dilutions of fresh dog corneal tissue as obtained over a period of 48 hours.

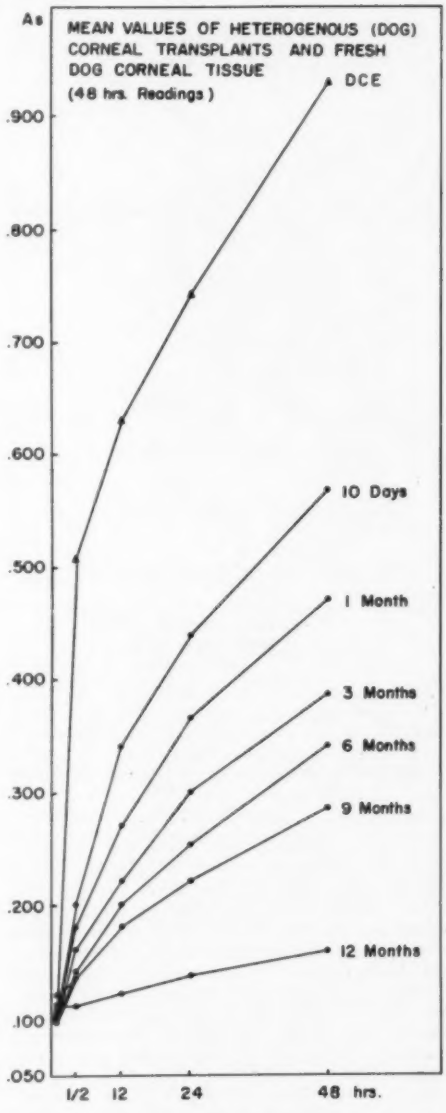


Fig. 11 (Geeraets, Lieb, Chan and Guerry). Mean values of the same six groups and fresh dog corneal tissue (DCE) as shown in Figure 9 with values obtained over 48 hours.

tures, particularly the corneal stroma. In perforating or lamellar grafts, the corneal epithelium is usually replaced by epithelium of the host within one week after transplantation. With this in mind and the additional fact that in the interlamellar technique the

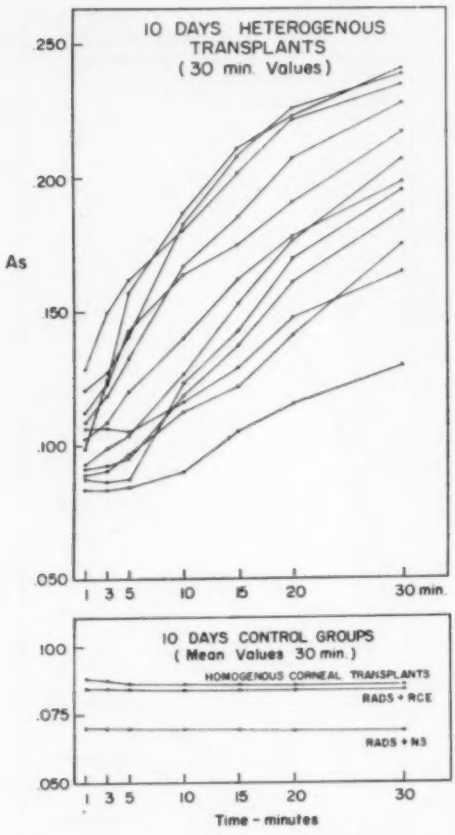


Fig. 12 (Geeraets, Lieb, Chan and Guerry). (Top) Turbidimetric readings of precipitin reactions of rabbit-antidog cornea serum with extract of heterogenous (dog) corneal grafts which had remained for 10 days in the rabbit cornea. Values were obtained over a period of 30 minutes. (Bottom) Mean values of control readings of 10-day-old homogenous corneal grafts and rabbit-antidog cornea serum (RADS), mean values of readings with normal saline (NS) and RADS, mean values of readings with RADS and fresh rabbit corneal extract (RCE).

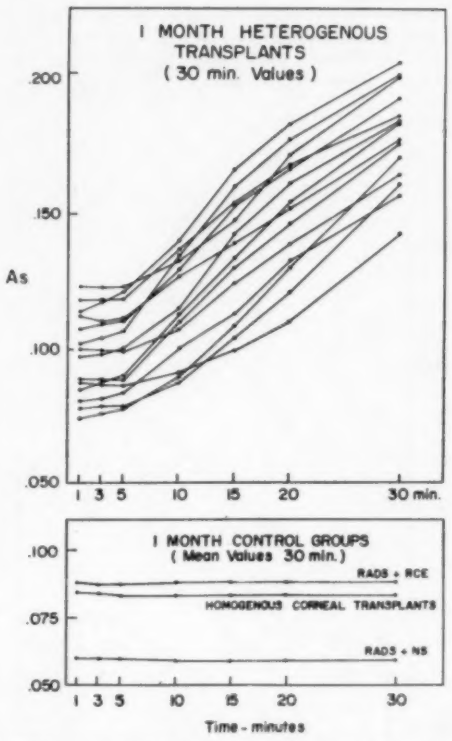


Fig. 13 (Geeraets, Lieb, Chan and Guerry). (Top) Turbidimetric readings of precipitin reactions of rabbit-antidog cornea serum with extract of heterogenous (dog) corneal grafts which had remained for one month in the rabbit cornea. Values were obtained over a period of 30 minutes. (Bottom) Mean values of control readings of one-month-old homogenous corneal grafts and rabbit-antidog cornea serum (RADS), mean values of readings with normal saline (NS) and RADS, mean values of readings with RADS and fresh rabbit corneal extract (RCE).

epithelium is placed between the stromal layers of the host cornea, one can consider that the epithelium may act as a toxic or mechanical irritant. This, in turn, may very well cause a more intense reaction and lead to a higher percentage of graft opacities than in those eyes where the epithelium has previously been removed. However, it was believed for the following reasons that the stronger reaction was caused by a stronger allergic response to the epithelium. If a corneal graft *without* epithelium was transplanted in the second eye of an animal in which, 10 days before, a graft *with* epithelium had been transplanted in the other eye, the second transplant showed earlier and more pronounced hypersensitive reaction than in animals in which grafts *without* epithelium had been used in both eyes. This finding does not prove unequivocally that

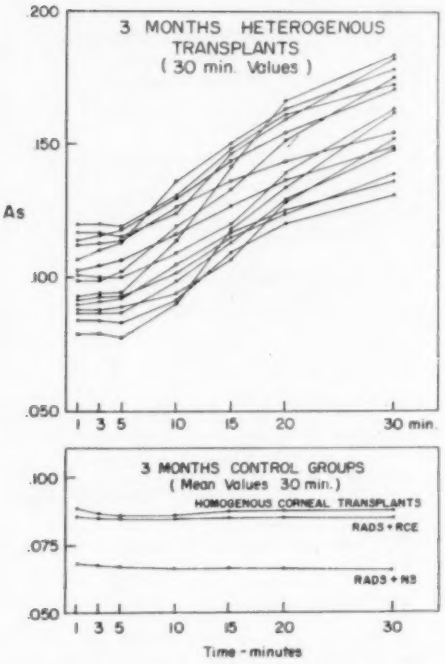


Fig. 14 (Geeraets, Lieb, Chan and Guerry). (Top) Turbidimetric readings of precipitin reactions of rabbit-antidog cornea serum with extract of heterogenous (dog) corneal grafts which had remained for three months in the rabbit cornea. Values were obtained over a period of 30 minutes. (Bottom) Mean values of control readings of three-month-old homogenous corneal grafts and rabbit-antidog cornea serum (RADS), mean values of readings with normal saline (NS) and RADS, mean values of readings with RADS and fresh rabbit corneal extract (RCE).

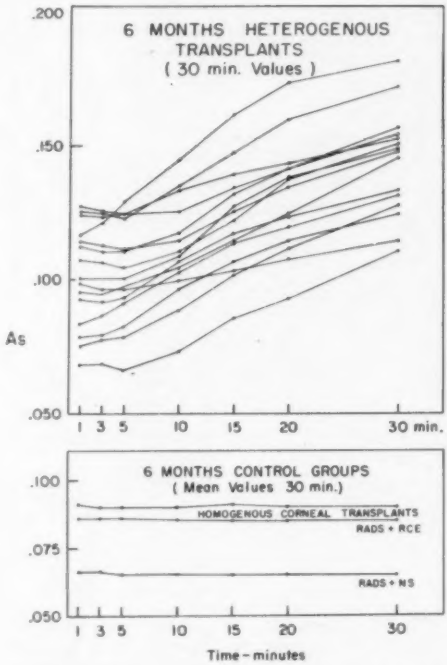


Fig. 15 (Geeraets, Lieb, Chan and Guerry). (Top) Turbidimetric readings of precipitin reactions of rabbit-antidog cornea serum with extract of heterogenous (dog) corneal grafts which had remained for six months in the rabbit cornea. Values were obtained over a period of 30 minutes. (Bottom) Mean values of control readings of six-month-old homogenous corneal grafts and rabbit-antidog cornea serum (RADS), mean values of readings with normal saline (NS) and RADS, mean values of readings with RADS and fresh rabbit corneal extract (RCE).

such changes are due to a higher antigenicity of corneal epithelium.

In their study on allergic reactions in keratoplasty, Lieb and Lerman demonstrated that, in those animals in which corneal stroma, which had previously been altered by freezing, was transplanted in the first eye, a more pronounced hypersensitive reaction occurred in a graft which was transplanted after 10 days in the second eye of the animal. The authors believe that the altered corneal stroma cells are more strongly antigenic and therefore stimulate a more intense antibody formation. If this is true, it could explain very well the more pronounced reaction in the second corneal transplant, where the stroma of the first graft had been altered by toxic or mechanical irritation due to epithelial degeneration within the stromal layers. A similar conclusion may be drawn from the observations of Klima (1949) in his study on antigenic properties of corneal proteins.

A more detailed discussion of the antigenicity of different corneal tissue structures will be given in a later paper.

In the control group of animals in which

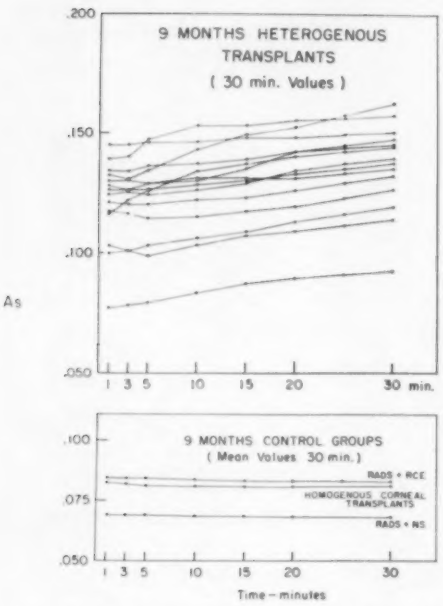


Fig. 16 (Geeraets, Lieb, Chan and Guerry). (Top) Turbidimetric readings of precipitin reactions of rabbit-antidog cornea serum with extract of heterogenous (dog) corneal grafts which had remained for nine months in the rabbit cornea. Values were obtained over a period of 30 minutes. (Bottom) Mean values of control readings of nine-month-old homogenous corneal grafts and rabbit-antidog cornea serum (RADS), mean values of readings with normal saline (NS) and RADS, mean values of readings with RADS and fresh rabbit corneal extract (RCE).

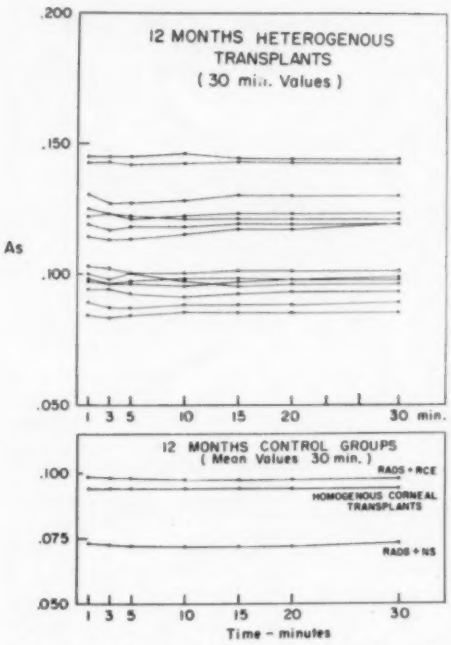


Fig. 17 (Geeraets, Lieb, Chan and Guerry). (Top) Turbidimetric readings of precipitin reactions of rabbit antidog-cornea serum with extract of heterogenous (dog) corneal grafts which had remained for 12 months in the rabbit cornea. Values were obtained over a period of 30 minutes. (Bottom) Mean values of control readings of 12-month old homogenous corneal grafts and rabbit-antidog cornea serum (RADS), mean values of readings with normal saline (NS) and RADS, mean values of readings with RADS and fresh rabbit corneal extract (RCE).

homogenous corneal grafts had been transplanted by the same technique, no haziness or opacities occurred.

In all grafts, heterogenous and homogenous, used in the present study, the epithelium had been removed before transplantation.

### Agar-diffusion technique

In the first experiment, the agar diffusion technique, in which a precipitation line forms within the agar at a certain distance between antigen depot and antibody, was used. The same rabbit-antidog serum which had been tested and found to be of highest specificity against dog corneal tissue was used in all experiments. Pure dog corneal tissue of the same measurements as had been used for transplantation was imbedded in the agar. The development of several precipitation lines could be observed after about 24 to 36 hours, if the agar plates were allowed to stay at room temperature. At 4°C. the first observable white precipitation line formed approximately after a period of three to five days. Since the rabbit-antidog serum was obtained from animals that had been sensitized with full-thickness dog cornea, a number of different specific antibodies were expected and could indeed be demonstrated. The different character of the specific antibodies

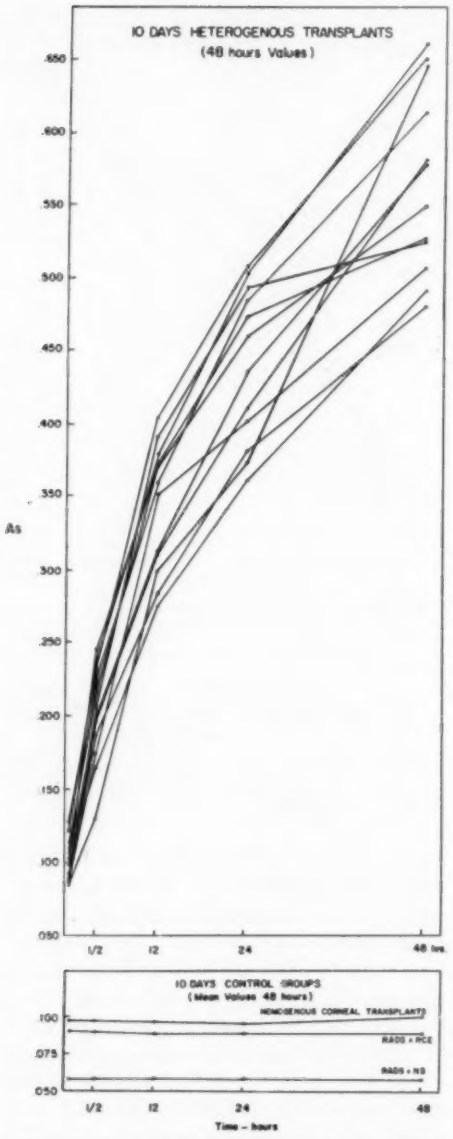


Fig. 18 (Geeraets, Lieb, Chan and Guerry). This represents the same group as in Figure 12 with readings over 48 hours.

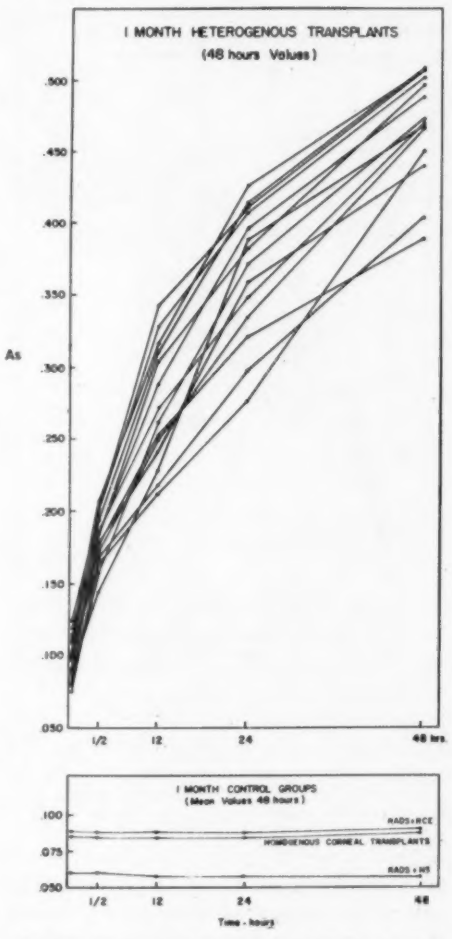


Fig. 19 (Geeraets, Lieb, Chan and Guerry). This represents the same group as in Figure 13 with readings over 48 hours.

shows up in different lines of antigen-antibody precipitates in the region of optimal proportions.

The serum was first checked in several controls against pure rabbit corneal tissue, rabbit homogenous transplants and normal saline. In addition other controls between normal rabbit serum and dog corneal tissue were carried out. No reaction occurred in any of the control tests up to three weeks and under different temperature conditions. In the main experiment, in each group of animals several corneal transplants were examined, with a homogenous corneal transplant for comparison. The homogenous

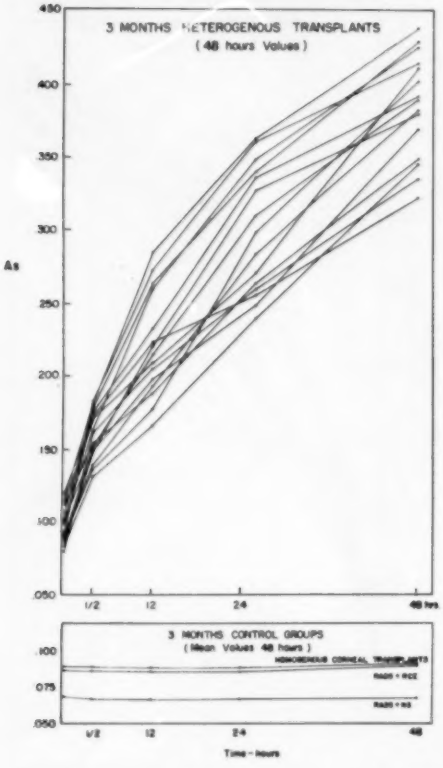


Fig. 20 (Geeraets, Lieb, Chan and Guerry). This represents the same group as in Figure 14 with readings over 48 hours.

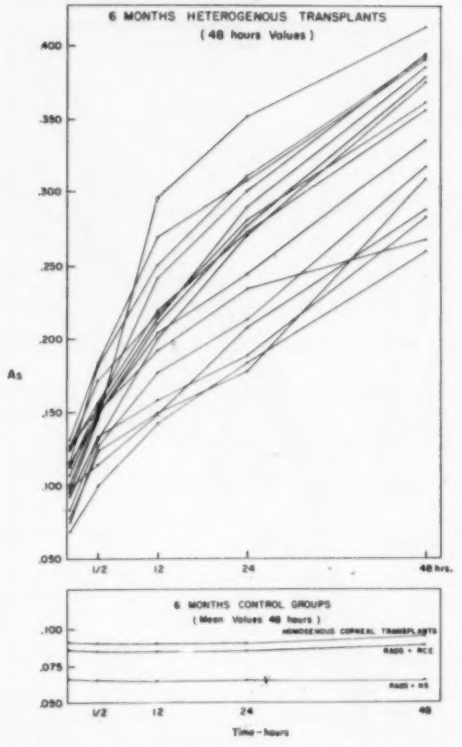


Fig. 21 (Geeraets, Lieb, Chan and Guerry). This represents the same group as in Figure 15 with readings over 48 hours.

grafts had remained in an experimental animal eye for the same length of time as the heterogenous transplants. In addition, full-thickness dog corneal tissue was embedded into the agar as a further control. While freshly obtained dog corneal tissue gave a strong reaction with the rabbit-antidog serum, the intensity of the reaction decreased rapidly if dog corneal tissue had been imbedded as a graft in the rabbit cornea for as short a period as 10 days (fig. 7). A reaction could not be demonstrated if the graft had remained in the host cornea for longer than 12 to 14 days.

The precipitation lines for the 10-day-old transplants were very faint. They appeared after approximately five to seven days at room temperature, somewhere between the area of the antiserum and the imbedded tissue of the heterogenous transplant. Usually after another two or three days, a second line could be made out which appeared very close to the imbedded tissue, concave with respect to the site of the antiserum. A serial dilution of the antiserum with normal saline or normal rabbit serum did not result in a more pronounced reaction compared with undiluted rabbit-antidog serum.

In none of the heterogenous transplants, which had remained in the rabbit eye over a longer period than two weeks, could a reaction be observed with this technique.

### Turbidimetric measurements

This more sensitive method was used

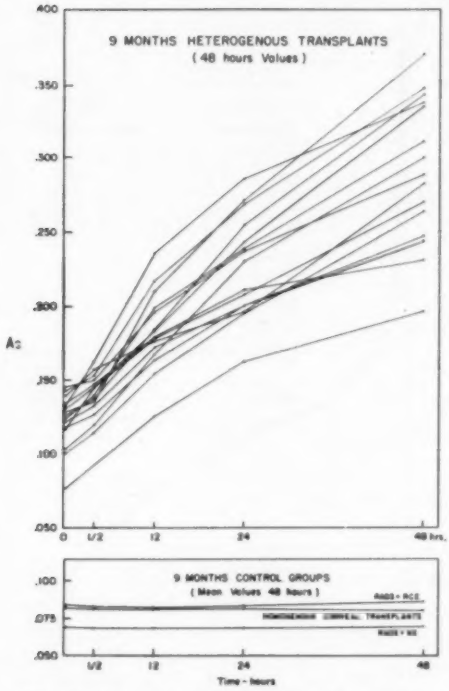


Fig. 22 (Geeraets, Lieb, Chan and Guerry). This represents the same group as in Figure 16 with readings over 48 hours.

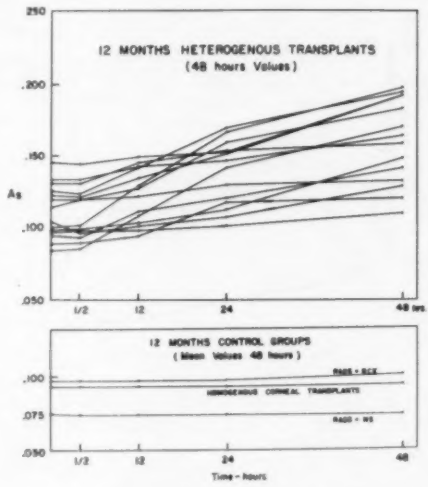


Fig. 23 (Geeraets, Lieb, Chan and Guerry). This represents the same group as in Figure 17 with readings over 48 hours.

along with the agar technique for determining precipitation. Since only minimal amounts of antigen were expected to be present, particularly in the corneal tissue which had remained in the experimental eyes for several months, serial dilutions did not seem to be justified. An effort was made, therefore, to obtain an approximate quantitative figure on the remaining donor protein by comparing the curves of absorbancy by the transplants as a function of time given with those of different known dilutions of fresh dog corneal extract. For this reason, pieces of corneal tissue exactly like those used in the previous transplantations were taken from freshly enucleated dog eyes and extracted with the same amount of normal saline as the grafts. The preparation, extraction, and so forth, were, of course, carried out under exactly the same conditions as those of the transplants. Figures 8 and 10 give the absorbancy curves constructed from mean values for different concentrations of pure dog corneal extract. Figures 12 to 23 show the different absorbancy curves which were obtained in the six main groups of animals, together with mean values of the control groups.

Antigen extracts from transplants, which had remained in the recipient eye over a period of 10 days, show a markedly decreased ability to precipitate with specific "antidog cornea serum" (figs. 12 and 18). Compared with the values obtained by using falling concentrations of fresh dog corneal extract, the shape of the curve is similar to those of a 1:8 to 1:16 dilution (figs. 8 and 10). This means that after a heterogenous graft has remained over a period of 10 days in the host cornea, it has lost most of its original ability to form a precipitable antigen-antibody complex.

From the turbidimetric measurements, one cannot reach any conclusion as to what antigens have disappeared; neither can one make quantitative estimates from the intensity of the lines appearing in the agar tech-

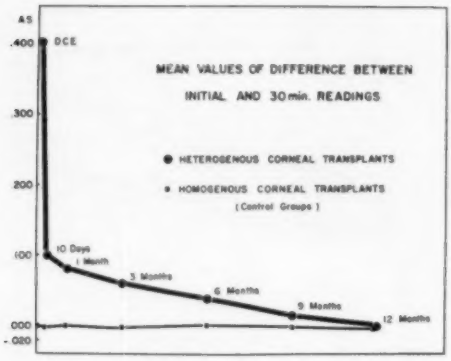


Fig. 24 (Geeraets, Lieb, Chan and Guerry). Mean absorbancy values of range differences between initial and 30-minute readings of the six groups of heterogenous (dog) corneal grafts compared with those of homogenous grafts as controls and fresh dog corneal tissue (DCE).

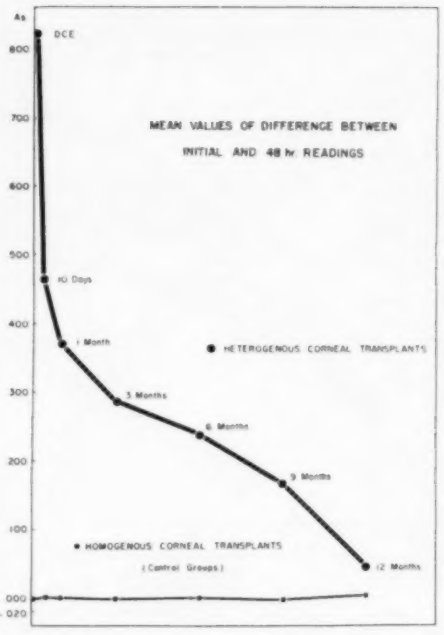


Fig. 25 (Geeraets, Lieb, Chan and Guerry). Mean absorbancy values of range differences between initial and 48-hour readings of the six groups of heterogenous (dog) corneal grafts compared with those of homogenous grafts as controls and fresh dog corneal tissue (DCE).

nique. But by using both results, one may venture to postulate that the bulk of the material which has disappeared according to the turbidimetric precipitin reaction corresponds to the material which failed to give precipitin lines in the agar technique.

After a period of two weeks to 12 months, there is a continued slow decrease in precipitable antigen.

A comparison of the values for the three months group (figs. 14 and 20) with those for the 6, 9 and 12 months group (figs. 15 to 17 and 21 to 23) shows a definite difference in the reaction curves for the first 30 minutes. The 48-hour values demonstrate a similar difference, but not as pronounced.

Quite a significant fall in the antigenic foreign protein can be observed in the 12-months group, but foreign protein is still clearly demonstrable (fig. 23).

Extracts from four additional transplants were used for precipitin reactions with serial dilutions of antiserum, but no significant difference was observed between these and reactions with undiluted serum. The degree of excess of antibody seemed, therefore, not to have an important influence on the values obtained. To exclude the possibility that the presence of rabbit corneal tissue in all extracts of transplanted dog cornea might have delayed a precipitin formation, controls were done with pure dog corneal extract to which pure rabbit corneal extract had been added in equal proportions. No difference in precipitin reaction could be observed. The differences between the initial absorbancy and the 30-minute and 48-hour values are easily shown by the means of the various groups (figs. 9, 11, 24, and 25 and tables 1 to 6).

The initial readings were taken 20 to 60 seconds after the serum and the extract had made contact in the cell. During this time, either no precipitation or only negligible reaction took place in the majority of the tests with transplant extracts. The initial reading can then be taken as the internal blank value when calculating the turbidity given by the specific precipitate. The difference between these initial absorbancy readings and the reading for the serum-saline blank was as-

TABLE 1

TURBIDIMETRIC PRECIPITIN TESTS

(Ten-day-old heterogenous transplants)*

| Transplant No. | Initial | 30-Minute Value | Difference | Initial | 48-Hour Value | Difference |
|---|---|---|---|---|---|---|
| 3 | 0.083 | 0.129 | 0.046 | 0.083 | 0.645 | 0.562 |
| 2 | 0.087 | 0.195 | 0.108 | 0.087 | 0.580 | 0.493 |
| 11 | 0.088 | 0.174 | 0.086 | 0.088 | 0.506 | 0.418 |
| 9 | 0.091 | 0.186 | 0.095 | 0.091 | 0.479 | 0.388 |
| 10 | 0.092 | 0.206 | 0.114 | 0.092 | 0.524 | 0.432 |
| 7 | 0.098 | 0.245 | 0.147 | 0.098 | 0.525 | 0.427 |
| 8 | 0.102 | 0.198 | 0.096 | 0.102 | 0.577 | 0.475 |
| 4 | 0.106 | 0.164 | 0.058 | 0.106 | 0.420 | 0.314 |
| 12 | 0.108 | 0.227 | 0.119 | 0.108 | 0.613 | 0.505 |
| 6 | 0.112 | 0.216 | 0.104 | 0.112 | 0.550 | 0.438 |
| 1 | 0.120 | 0.238 | 0.118 | 0.120 | 0.660 | 0.540 |
| 5 | 0.128 | 0.234 | 0.106 | 0.128 | 0.710 | 0.582 |
| Means | 0.101 | 0.201 | 0.100 | 0.101 | 0.566 | 0.465 |
| Remarks | | | Highest Value 0.147<br>Lowest Value 0.046 | | | Highest Value 0.582<br>Lowest Value 0.314 |

* The initial, 30-minute and 48-hour values only, the differences for each examined eye and the means of the group are given.

cribed to turbidity of the cornea extract. The latter contributed about as much to the absorbancy as the serum blank. The more concentrated dog cornea extracts reacted so rapidly with the antiserum that it was impossible to measure the initial turbidity contribution by the serum and the unreacted extract. In these instances the average initial value of the six other groups, being 0.105As, was used as the internal blank reading and subtracted from the 30-minute and 48-hour values. The absorbancies for the specific precipitates, calculated by subtracting the initial value from the 30-minute and 48-hour values, are shown in Tables 1 to 6 for the six groups of animals.

TABLE 2

TURBIDIMETRIC PRECIPITIN TESTS

(One-month-old heterogenous transplants)*

| Transplant No. | Initial | 30-Minute Value | Difference | Initial | 48-Hour Value | Difference |
|---|---|---|---|---|---|---|
| 6 | 0.074 | 0.172 | 0.098 | 0.074 | 0.468 | 0.394 |
| 7 | 0.078 | 0.162 | 0.084 | 0.078 | 0.450 | 0.372 |
| 8 | 0.080 | 0.157 | 0.077 | 0.080 | 0.472 | 0.392 |
| 3 | 0.085 | 0.184 | 0.099 | 0.085 | 0.488 | 0.403 |
| 10 | 0.087 | 0.193 | 0.106 | 0.087 | 0.468 | 0.381 |
| 12 | 0.089 | 0.176 | 0.087 | 0.089 | 0.389 | 0.300 |
| 5 | 0.097 | 0.183 | 0.086 | 0.097 | 0.500 | 0.403 |
| 13 | 0.100 | 0.169 | 0.069 | 0.100 | 0.404 | 0.304 |
| 4 | 0.102 | 0.202 | 0.100 | 0.102 | 0.497 | 0.395 |
| 9 | 0.107 | 0.193 | 0.086 | 0.107 | 0.509 | 0.402 |
| 14 | 0.112 | 0.178 | 0.066 | 0.112 | 0.439 | 0.327 |
| 11 | 0.114 | 0.206 | 0.092 | 0.114 | 0.507 | 0.393 |
| 1 | 0.118 | 0.186 | 0.068 | 0.118 | 0.470 | 0.352 |
| 2 | 0.123 | 0.201 | 0.078 | 0.123 | 0.501 | 0.378 |
| Means | 0.097 | 0.180 | 0.083 | 0.097 | 0.469 | 0.372 |
| Remarks | | | Highest Value 0.106<br>Lowest Value 0.066 | | | Highest Value 0.403<br>Lowest Value 0.300 |

TABLE 3

TURBIDIMETRIC PRECIPITIN TESTS

(Three-month-old heterogenous transplants)*

| Transplant No. | Initial | 30-Minute Value | Difference | Initial | 48-Hour Value | Difference |
|---|---|---|---|---|---|---|
| 8 | 0.079 | 0.162 | 0.083 | 0.079 | 0.335 | 0.256 |
| 15 | 0.084 | 0.131 | 0.047 | 0.084 | 0.345 | 0.261 |
| 4 | 0.087 | 0.148 | 0.061 | 0.087 | 0.380 | 0.293 |
| 1 | 0.088 | 0.152 | 0.064 | 0.088 | 0.390 | 0.302 |
| 9 | 0.090 | 0.136 | 0.046 | 0.090 | 0.403 | 0.313 |
| 5 | 0.092 | 0.139 | 0.047 | 0.092 | 0.383 | 0.291 |
| 7 | 0.093 | 0.183 | 0.090 | 0.093 | 0.415 | 0.322 |
| 11 | 0.099 | 0.175 | 0.076 | 0.099 | 0.393 | 0.294 |
| 2 | 0.101 | 0.163 | 0.062 | 0.101 | 0.426 | 0.325 |
| 12 | 0.103 | 0.149 | 0.046 | 0.103 | 0.370 | 0.267 |
| 6 | 0.107 | 0.178 | 0.071 | 0.107 | 0.430 | 0.323 |
| 3 | 0.112 | 0.154 | 0.042 | 0.112 | 0.349 | 0.237 |
| 13 | 0.114 | 0.171 | 0.057 | 0.114 | 0.412 | 0.298 |
| 10 | 0.117 | 0.182 | 0.065 | 0.117 | 0.439 | 0.322 |
| 14 | 0.120 | 0.172 | 0.052 | 0.120 | 0.322 | 0.202 |
| Means | 0.099 | 0.160 | 0.061 | 0.099 | 0.386 | 0.287 |
| Remarks | | | Highest Value 0.009<br>Lowest Value 0.042 | | | Highest Value 0.325<br>Lowest Value 0.202 |

Both the 30-minute and the 48-hour values decrease with the length of time the transplant had remained in the host cornea. The difference between groups was greatest between the control group of fresh dog cornea and the 10-day-old heterogenous transplants. Thereafter, the differences between the remaining groups of 1, 3, 6, 9, and 12 months were relatively small.

The results obtained by immunochemical analysis demonstrate that substances of transplanted heterogenous corneal grafts are still present within the host tissue after a period of 12 months. Although this study does not

TABLE 4

TURBIDIMETRIC PRECIPITIN TESTS

(Six-month-old heterogenous transplants)*

| Transplant No. | Initial | 30-Minute Value | Difference | Initial | 48-Hour Value | Difference |
|---|---|---|---|---|---|---|
| 4 | 0.068 | 0.100 | 0.032 | 0.068 | 0.259 | 0.191 |
| 12 | 0.075 | 0.127 | 0.052 | 0.075 | 0.317 | 0.242 |
| 5 | 0.078 | 0.124 | 0.046 | 0.078 | 0.308 | 0.230 |
| 8 | 0.083 | 0.131 | 0.048 | 0.083 | 0.375 | 0.292 |
| 6 | 0.092 | 0.113 | 0.041 | 0.092 | 0.282 | 0.190 |
| 11 | 0.095 | 0.145 | 0.050 | 0.095 | 0.412 | 0.317 |
| 1 | 0.098 | 0.114 | 0.016 | 0.098 | 0.287 | 0.189 |
| 10 | 0.107 | 0.150 | 0.043 | 0.107 | 0.267 | 0.160 |
| 3 | 0.100 | 0.148 | 0.048 | 0.100 | 0.335 | 0.235 |
| 15 | 0.112 | 0.154 | 0.042 | 0.112 | 0.394 | 0.282 |
| 2 | 0.124 | 0.156 | 0.032 | 0.124 | 0.356 | 0.232 |
| 14 | 0.125 | 0.171 | 0.046 | 0.125 | 0.361 | 0.236 |
| 16 | 0.127 | 0.152 | 0.025 | 0.127 | 0.385 | 0.258 |
| 13 | 0.114 | 0.147 | 0.033 | 0.114 | 0.378 | 0.264 |
| 7 | 0.116 | 0.181 | 0.065 | 0.116 | 0.393 | 0.277 |
| Means | 0.101 | 0.141 | 0.040 | 0.101 | 0.341 | 0.240 |
| Remarks | | | Highest Value 0.065<br>Lowest Value 0.016 | | | Highest Value 0.317<br>Lowest Value 0.160 |

TABLE 5

TURBIDIMETRIC PRECIPITIN TESTS

(Nine-month-old heterogenous transplants)*

| Transplant No. | Initial | 30-Minute Value | Difference | Initial | 48-Hour Value | Difference |
|---|---|---|---|---|---|---|
| 1 | 0.077 | 0.092 | 0.015 | 0.077 | 0.196 | 0.119 |
| 16 | 0.100 | 0.114 | 0.014 | 0.100 | 0.264 | 0.164 |
| 5 | 0.103 | 0.119 | 0.016 | 0.103 | 0.300 | 0.197 |
| 10 | 0.116 | 0.144 | 0.018 | 0.116 | 0.270 | 0.154 |
| 3 | 0.121 | 0.132 | 0.011 | 0.121 | 0.244 | 0.123 |
| 7 | 0.128 | 0.135 | 0.007 | 0.128 | 0.370 | 0.242 |
| 6 | 0.130 | 0.145 | 0.015 | 0.130 | 0.335 | 0.205 |
| 12 | 0.134 | 0.147 | 0.013 | 0.134 | 0.231 | 0.097 |
| 11 | 0.139 | 0.157 | 0.018 | 0.139 | 0.282 | 0.143 |
| 2 | 0.145 | 0.150 | 0.005 | 0.145 | 0.288 | 0.143 |
| 8 | 0.124 | 0.139 | 0.015 | 0.124 | 0.311 | 0.187 |
| 13 | 0.126 | 0.137 | 0.011 | 0.126 | 0.343 | 0.217 |
| 4 | 0.132 | 0.162 | 0.030 | 0.132 | 0.337 | 0.205 |
| 14 | 0.117 | 0.126 | 0.009 | 0.117 | 0.247 | 0.130 |
| Means | 0.121 | 0.136 | 0.015 | 0.121 | 0.287 | 0.166 |
| Remarks | | | Highest Value 0.030<br>Lowest Value 0.005 | | | Highest Value 0.242<br>Lowest Value 0.097 |

answer the question concerning the actual amount of remaining donor tissue, it shows the behavior of the graft in its ability to act as a specific antigen. A loss of certain antigenic patterns due to acquired adaptation of the host tissue was excluded by performing studies in vitro. In this way, the results obtained might actually suggest that the loss of precipitation ability of the graft proteins is an expression of actual loss of graft substance.

It seemed to us that a comparison of observed clinical changes in corneal transplants, experimental studies in vivo and in vitro lead to very similar conclusions. The extensive work by Maumenee, et al., on hyper-

TABLE 6

TURBIDIMETRIC PRECIPITIN TESTS

(Twelve-month-old heterogenous transplants)*

| Transplant No. | Initial | 30-Minute Value | Difference | Initial | 48-Hour Value | Difference |
|---|---|---|---|---|---|---|
| 11 | 0.084 | 0.085 | 0.001 | 0.084 | 0.170 | 0.086 |
| 9 | 0.089 | 0.089 | 0.000 | 0.089 | 0.120 | 0.031 |
| 10 | 0.094 | 0.093 | −0.001 | 0.094 | 0.141 | 0.047 |
| 14 | 0.097 | 0.098 | 0.091 | 0.097 | 0.110 | 0.013 |
| 6 | 0.098 | 0.099 | 0.001 | 0.098 | 0.148 | 0.050 |
| 1 | 0.100 | 0.101 | 0.001 | 0.100 | 0.197 | 0.097 |
| 7 | 0.103 | 0.096 | −0.007 | 0.103 | 0.128 | 0.025 |
| 8 | 0.114 | 0.119 | 0.005 | 0.114 | 0.183 | 0.069 |
| 13 | 0.119 | 0.119 | 0.000 | 0.119 | 0.132 | 0.013 |
| 5 | 0.122 | 0.121 | −0.001 | 0.122 | 0.192 | 0.070 |
| 12 | 0.125 | 0.123 | −0.002 | 0.125 | 0.194 | 0.069 |
| 2 | 0.130 | 0.130 | 0.000 | 0.130 | 0.158 | 0.028 |
| 4 | 0.145 | 0.144 | −0.001 | 0.145 | 0.192 | 0.047 |
| 3 | 0.133 | 0.133 | 0.000 | 0.133 | 0.164 | 0.031 |
| Means | 0.1110 | 0.1108 | −0.0002 | 0.111 | 0.159 | 0.048 |
| Remarks | | | Highest Value +0.005<br>Lowest Value −0.007 | | | Highest Value 0.097<br>Lowest Value 0.013 |

sensitivity studies in corneal transplants has shown that an early transplantation of additional specific antigenic material into a host, in which at the same time a corneal graft is performed, gives a stronger hypersensitive reaction on the graft. Such a reaction develops usually between the second and fourth week after transplantation. If additional specific antigenic tissue is transplanted at a later date, no increased allergic reaction can be observed in the corneal graft. These clinical observations were explained earlier as being caused by replacement of the stroma cells by cells of the host tissue which therefore do not show allergic reaction with the specific antibody.

With regard to this explanation, the results of the present study suggest that the clinical findings could be related to the very rapid loss of antigenic properties after transplantation of corneal tissue. The short time of eight to 10 days in which those changes occur certainly excludes the possibility that the stromal cells could have been completely replaced by the host, but suggests that in addition another highly antigenic substance decreases very rapidly. On the other hand, the still demonstrable specific antigen-antibody complex formation of transplanted corneal tissue, after it has remained in the host tissue for a period of one year, shows that certain substances of the transplant retain their individual characteristics.

Recent studies with radioactive labeled corneal transplants by Dohlman, Smelser, et al., have shown that there is an early loss of the interfibrillar ground substance and that the stroma fibers are not replaced over a period of 40 days. These findings suggest that there could be a relationship between interfibrillar ground substance and the early considerable loss of precipitin formation. The very slow decreasing rate of change of remaining precipitin formation might well be caused by the stroma fibers. Such changes would, in addition, explain why preserved corneal tissue seems to have less antigenicity compared with freshly obtained corneal grafts for transplantation.

## Summary

Corneal tissue obtained from dog eyes was transplanted into 104 rabbit eyes by employing an interlamellar technique. The transplants were then removed at different periods of time from 10 days to 12 months after transplantation. The remaining foreign protein was determined immunologically by the agar-diffusion technique and by turbidimetric measurements. Controls with homogenous corneal grafts were done on 36 rabbit eyes.

The results show that the graft substances lose most of their ability to form specific precipitates during the first 10 days of their transplantation into the host tissue. After this time, there is still a further decrease in immunologically reactive substances, but at a slower rate. After an observation time of one year, there was still foreign protein present in the host corneas.

It is suggested that the early loss of reacting protein from the grafts might be related to the relatively early loss of the interlamellar ground substance and stroma cells, while the prolonged precipitin reaction over a period of one year might be related to the stroma fibers.

The literature concerned with experimental studies of corneal grafts is discussed.

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# THE ELECTROENCEPHALOGRAM IN RETINITIS PIGMENTOSA*

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Retinitis pigmentosa is frequently associated with neurologic and endocrinologic disorders. Among the associated conditions mentioned in the literature are various degrees of deafness, congenital deaf-mutism, mental deficiency, schizophrenia, paranoia, various types of epilepsy, oligophrenia, pituitary disturbances such as the Laurence-Moon-Biedl syndrome and diabetes insipidus,[1–3] spastic quadriplegia,[4] familial paraplegia,[5] spinocerebellar degenerations,[6] cerebral atrophy,[7] Gaucher's disease,[8] and multiple sclerosis.[9] In addition, hereditary neurologic conditions have been reported in one member of a family and retinitis pigmentosa or some form of tapetoretinal degeneration in another member.[10]

Because of these associations, a number of investigators have studied the electrocephalogram (EEG) in tapetoretinal degenerations. François and others reported electroencephalographic findings in 19 cases of retinitis pigmentosa in 1954,[11] Streifler and Landau, 25 cases in 1955,[12] and Cordier, Dureux, and Barbier, 17 cases in 1956.[10]

The present study was undertaken to determine whether a complete electroencephalographic evaluation including sleep recordings could reveal any characteristic patterns in patients with retinitis pigmentosa; also, if any diagnostic value could be ascribed to this test.

The sleep record adds to the value of electroencephalographic examinations since a greater proportion of abnormalities, particularly those related to seizure or discharging phenomenon, became manifest in this state.[13–15] A study, for example, of patients with retrolental fibroplasia revealed more than twice as many abnormalities during sleep than in the awake state.[16] Sleep records may also be of more value in detecting subcortical abnormalities since it has been shown in animals that normal sleep patterns originate in the thalamus and hypothalamus,[17] and in humans that the manifestations of capsular, thalamic and diencephalic epilepsy are almost never seen except in sleep.[18] Previous investigators of the electroencephalogram in retinitis pigmentosa did not include sleep recordings.

## MATERIALS

The patients selected for this study fulfilled the following requirements: (1) typical fundus findings of retinis pigmentosa, (2) no history of acute systemic infections immediately before the onset of ocular symptoms, (3) no evidence of chronic infections such as syphilis, (4) the finding of an extinguished electroretinogram, and (5) no history suggesting any type of epilepsy or

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definite known cause of brain-wave abnormalities.

In all, there were 21 male and 11 female patients. The relevant data are shown in Table 1. Five families contributed 10 of the 32 cases and three other patients had possibly other relatives affected with the disease. It is noteworthy that 11 of the 32 cases had associated neurologic or endocrinologic findings and by clinical criteria four of these cases were diagnosed as the Laurence-Moon-Biedl syndrome. One patient was unusual in that she also met criteria two to five, but criterion one only with regard to one eye.[19]

## Methods

Recordings were made with a Grass 8 channel electroencephalograph. A monopolar recording technique with the ears as reference points was used. Silver discs fastened to the scalp with collodion in at least eight different areas served as electrodes (fig. 1). The recorder was calibrated to give a seven-mm. excursion for 50 micro volts; the paper speed was 30 mm. per second.

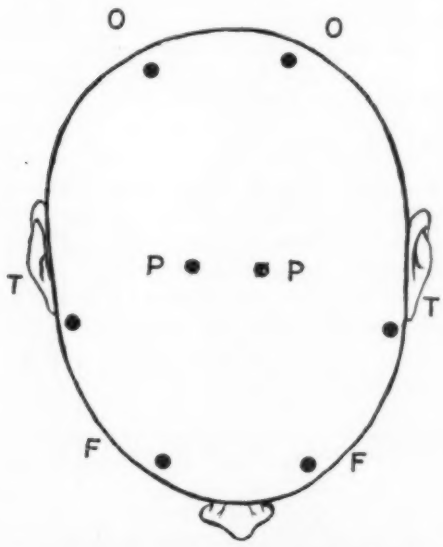


Fig. 1 (Krill and Stamps). Electrode placement showing basic eight leads used in every patient.

In addition to awake records, sleep records were obtained in all cases but one. In the majority of cases Seconal or chloral hydrate was necessary to produce sleep. The effects of these drugs on the electroencephalogram are well known.[14]

Included in this study were the observations of (1) the phenomenon of blocking the alpha waves by eliciting the examinee's attention or by having him open his eyes, and (2) the effect of hyperventilation (50 breaths a minute for two minutes). Alpha blocking was evaluated in 26 patients and hyperventilation effects were observed in 12 patients.

## Interpretation

In the analysis of the records the age and state of consciousness of the patient were taken into careful consideration.[14] Electroencephalographic patterns considered to be abnormal were: (1) focal or diffuse seizure discharges, (2) focal or diffuse slow waves, (3) extreme fast activity, and (4) asymmetry of activity. Records were classified as normal, mildly abnormal, and abnormal.

The alpha wave amplitude is ordinarily considered a factor of secondary importance in as much as its voltage varies greatly in the normal population. Because of the emphasis by François, Stefans, and DeRouck on the finding of low-voltage alpha waves as a characteristic of retinitis pigmentosa,[11] the present group was studied particularly from this standpoint. All alpha voltages were determined before any barbiturate administration and after arousal. The records were divided into three groups, namely good or prominent alpha voltage (fig. 2), low-voltage alpha waves (fig. 3), and flat records (fig. 4). The low voltage group was characterized by alpha amplitude usually not exceeding 25 microvolts and waves of a predominately fast frequency. In the groups of flat recordings the alpha response was barely distinguishable from the baseline and no dominant alpha frequency could be ascertained.

In the evaluation of the effects of hyper-

TABLE 1

CLINICAL AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS IN RETINITIS PIGMENTOSA CASES

| Case | Age (yr.) | Age at Onset of Symptoms (yr.) | Family History | Associated Findings | EEG Findings |
|---|---|---|---|---|---|
| 1 | 36 | 21 | | Speech impediment, hearing difficulty | Nor LV |
| 2 | 16 | 1? | | | Nor GV |
| 3 | 48 | 44 | | | Nor GV |
| 4 | 54 | 49 | | Partial deafness | Nor GV |
| 5 | 21 | 13 | Brother of Case 6 | Speech impediment, partial deafness | Nor GV |
| 6 | 18 | 10 | Brother of Case 5 | Speech impediment, partial deafness | M.Abn GV |
| 7 | 24 | 6? | Brother of Case 8 | Laurence-Moon-Biedl syndrome | M.Abn GV |
| 8 | 16 | 6? | Brother of Case 7 | Laurence-Moon-Biedl syndrome | Nor GV |
| 9 | 8 | 6? | Sister of Case 10 | Laurence-Moon-Biedl syndrome | Nor GV |
| 10 | 15 | <10 | Sister of Case 9 | Laurence-Moon-Biedl syndrome | Nor GV |
| 11 | 34 | 7 | Parents were third cousins | | M.Abn GV |
| 12 | 53 | 47 | | | M.Abn GV |
| 13 | 56 | 47 | | | Nor GV |
| 14 | 18 | <10 | Brother of Case 16 | | Nor GV |
| 15 | 13 | <10 | Brother of Case 15 | | Nor GV |
| 16 | 29 | 19 | | | Nor GV |
| 17 | 38 | 8 | Sister of Case 29, 3 sisters with retinitis pigmentosa | | M.Abn LV |
| 18 | 50 | 30 | 2 brothers, cousin and grandfather with hemeralopia | | Nor GV |
| 19 | 40 | <30 | | Partial deafness, behavior disorder | Abn LV |

Nor: Normal.
M.Abn: Mildly abnormal.
Abn: Abnormal.
GV: Good voltage.
LV: Low voltage.

TABLE 1 (*Continued*)

| Case | Age (yr.) | Age at Onset of Symptoms (yr.) | Family History | Associated Findings | EEG Findings |
|---|---|---|---|---|---|
| 20 | 37 | 26 | | | Nor LV |
| 21 | 32 | 2? | | | Abn GV |
| 22 | 35 | <10 | | | Nor GV |
| 23 | 58 | 50 | | Deafness, speech impediment, spasticity | Nor LV |
| 24 | 56 | 44 | | | Nor Flat |
| 25 | 29 | 23 | Sister had retinitis pigmentosa | | Nor GV |
| 26 | 42 | 28 | | | Nor GV |
| 27 | 57 | 32 | Mother had retinitis pigmentosa, parents were second cousins | | Nor GV |
| 28 | 35 | 8 | Sister of Case 18 | | Nor GV |
| 29 | 55 | 50 | | | Nor LV |
| 30 | 17 | 6 | | Mental deficiency | Nor GV |
| 31 | 59 | 9 | | Deafness, speech impediment | Nor GV |
| 32 | 42 | <10 | Family history of nightblindness | | Nor GV |

ventilation, the precipitation of seizure activity was considered as definitely abnormal. The findings of large amplitude slow waves during or after hyperventilation has been known as a build-up, the degree of which varies with such factors as the blood concentration of carbon dioxide, oxygen, or glucose, and fatigue, drowsiness, and body temperature.[14, 25] A larger build-up than expected from an evaluation of the associated factors was considered to be abnormal.

## Results

Of the total of 32 cases of retinitis pigmentosa seven were considered to have abnormal electroencephalograms. Of these, five were classified as mildly abnormal (Cases 6, 7, 11, 12, and 17) and two as definitely abnormal (Cases 19 and 21). The mildly abnormal recordings showed seizure activity classified as: (1) six per second positive spike seizure activity in three cases (figs. 5, 6, and 7), (2) 14 and six per second positive spike seizure activity in one case (fig. 8), and (3) six per second spike and wave seizure activity in the remaining case (fig. 9). One of the abnormal records revealed a mixed fast and slow background with a good deal of spike and wave seizure discharges showing up most prominently in the frontal-

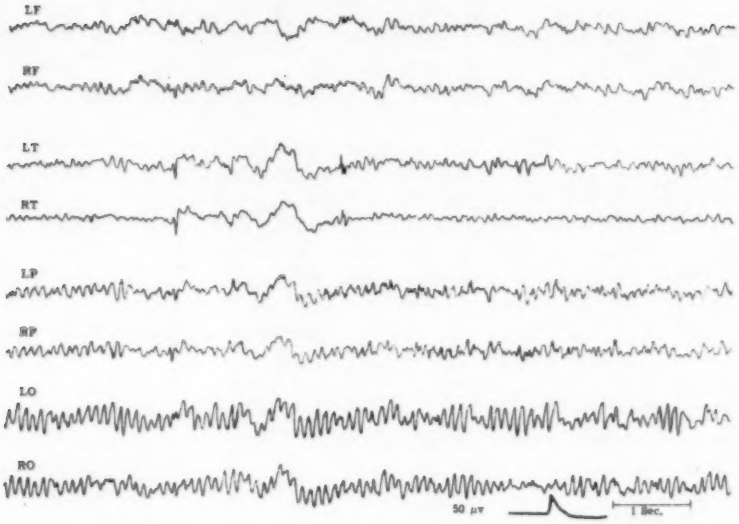


Fig. 2 (Krill and Stamps). Normal alpha waves are shown in left occipital (LO) and right occipital (RO) leads.

parietal areas during drowsiness and sleep (fig. 10). In the other abnormal record long runs of diffuse slow waves of five to seven per second frequency were noted primarily during drowsiness (fig. 11).

With regard to the amplitude of the alpha waves 25 records were placed in the category of good or prominent alpha, six in the category of low-voltage alpha waves, and one in the category of flat recordings.

Some degree of alpha blocking was observed in 18 patients, while four patients

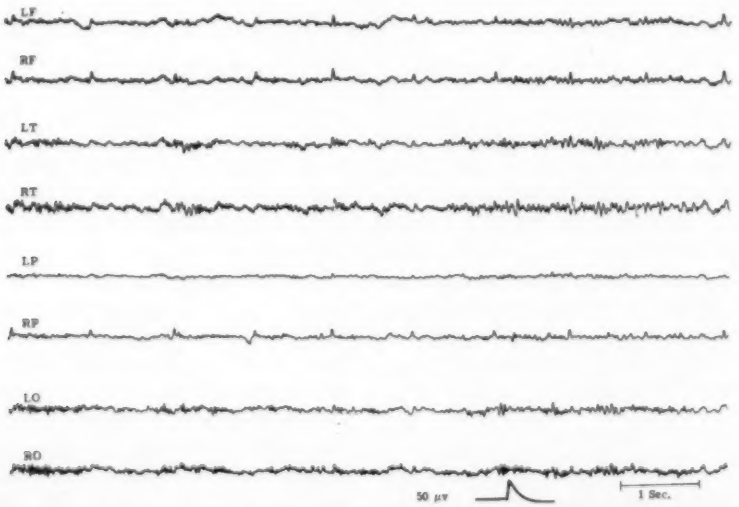


Fig. 3 (Krill and Stamps). Low-voltage alpha waves are shown in LO and RO leads.

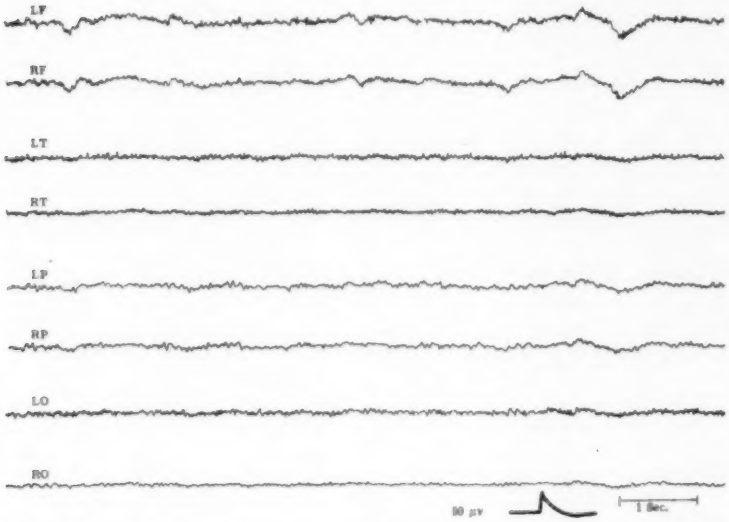


Fig. 4 (Krill and Stamps). Flat record. No alpha waves are seen in LO and RO leads.

showed no effect. Six of the seven records in the categories of low-voltage or flat waves could not be adequately evaluated, even with an increase in gain. No relationship could be determined between the degree or absence of alpha blocking and the visual status of the patient.

Hyperventilation of 12 patients proved to be of no value in this study since no additional abnormalities could be detected and build-ups were absent or minimal.

## Comment

While the percentage of abnormalities in

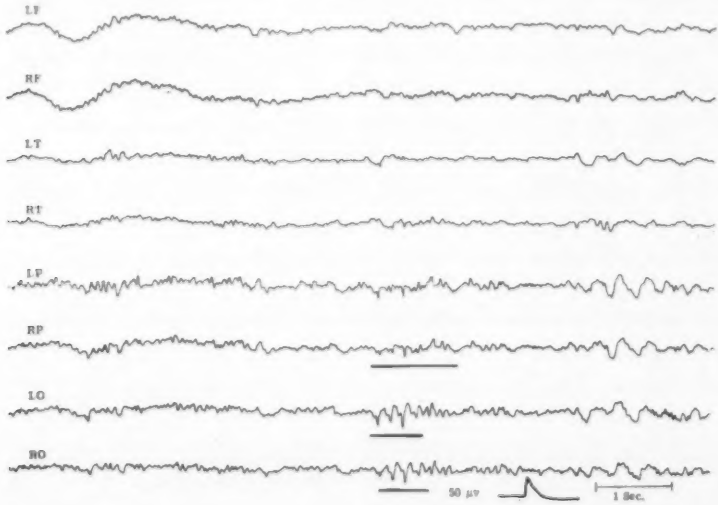


Fig. 5 (Krill and Stamps). Six per second positive spike activity is underlined.

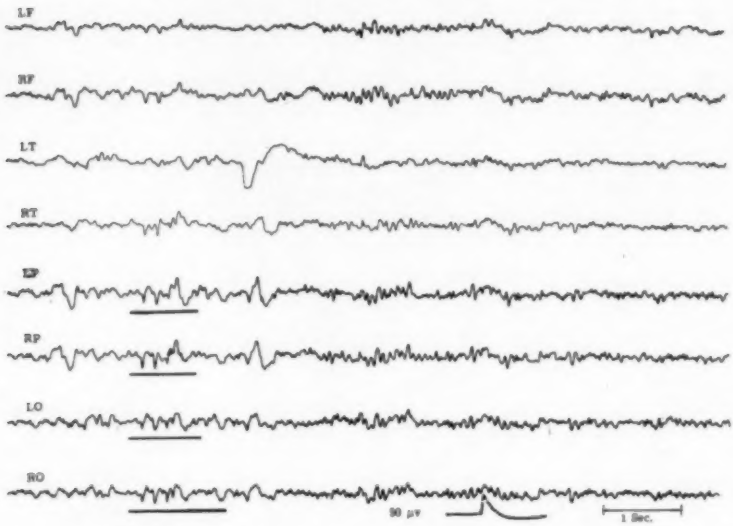


Fig. 6 (Krill and Stamps). Six per second positive spike activity is underlined.

our group of 32 patients was only 22 percent, the types of abnormalities encountered seemed to be significant.

The abnormalities classified as mild were all found primarily during drowsiness or sleep. This is consistent with previous experience concerning these abnormalities. In a series of 300 cases showing 14 and six per second positive spike seizure discharge activity only three percent revealed this pattern during the awake state,[17] and almost all of a series of 210 records with six per second

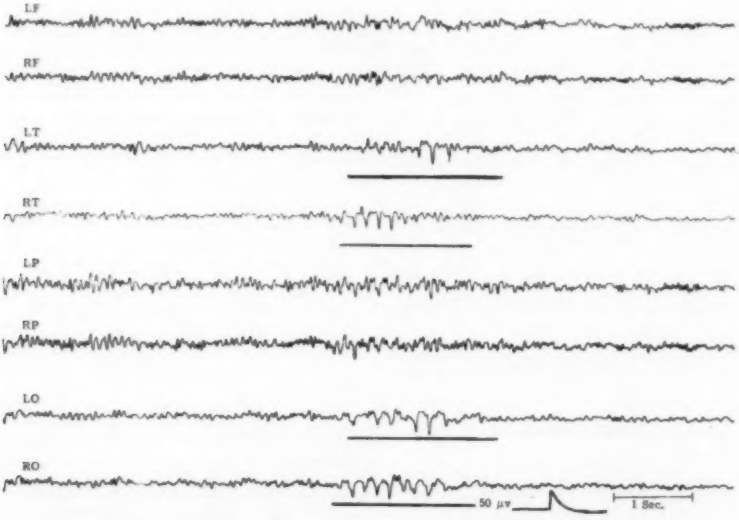


Fig. 7 (Krill and Stamps). Six per second positive spike activity is underlined.

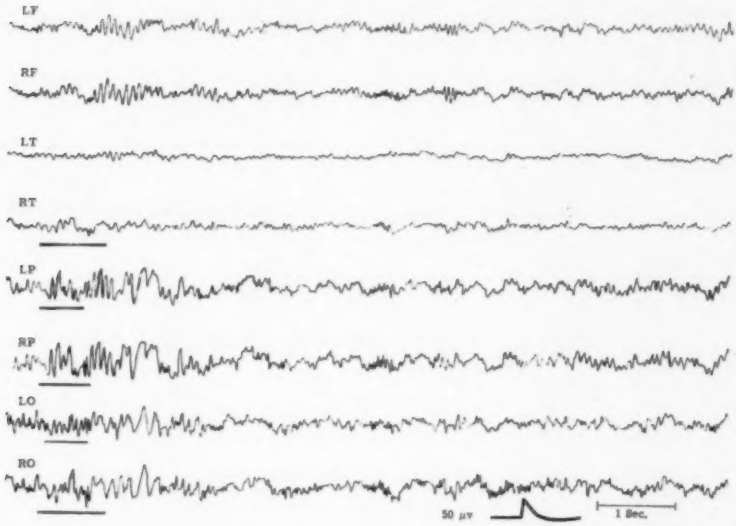


Fig. 8 (Krill and Stamps). Fourteen per second positive spike activity is underlined.

spike and wave patterns revealed this finding primarily during drowsiness or very light sleep.[20]

The same findings were observed primarily in adolescents and young adults.[17, 20] In an analysis of 320 normal controls aged 25 years or older, Gibbs and Gibbs found only six cases with 14 and six per second positive spikes.[21] In our series three of the four patients with this finding (Cases 11, 12, and 17) were beyond 30. Six per second spike and wave discharge activity, generally, is a

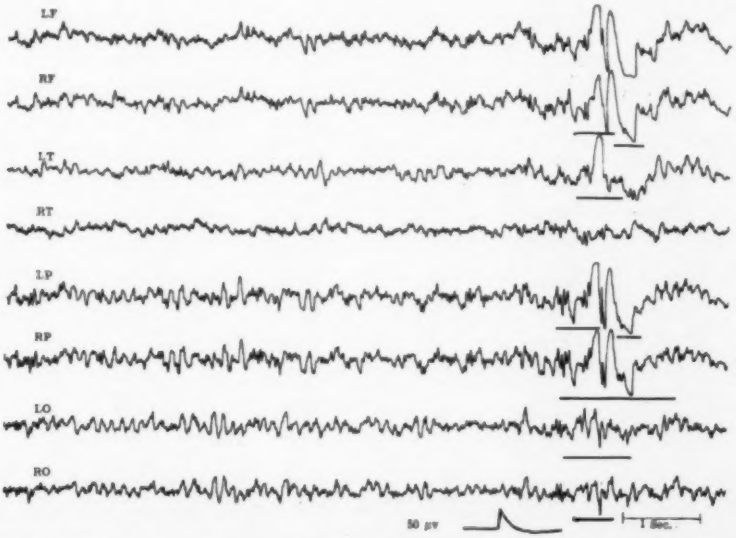


Fig. 9 (Krill and Stamps). Six per second spike and wave seizure activity are underlined.

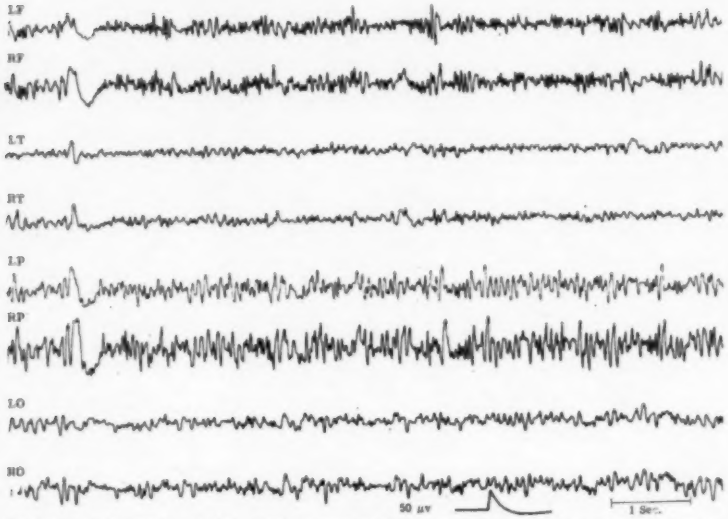


Fig. 10 (Krill and Stamps). A fast background with some spike and wave seizure discharges is seen predominately in the frontal (LF, RF) and parietal (LP, RP) leads. The slow background is not seen on this page of the record.

rare finding. In reviewing 30,000 normal and abnormal patients Thomas found only 210 cases with this pattern.[20]

All of these mildly abnormal patterns are thought to relate to subcortical foci since they are characterized by positive spikes and show up primarily during sleep or drowsiness.[13, 17]

The diffuse slow activity noted in Case 19 is a pattern known to occur in diffuse or-

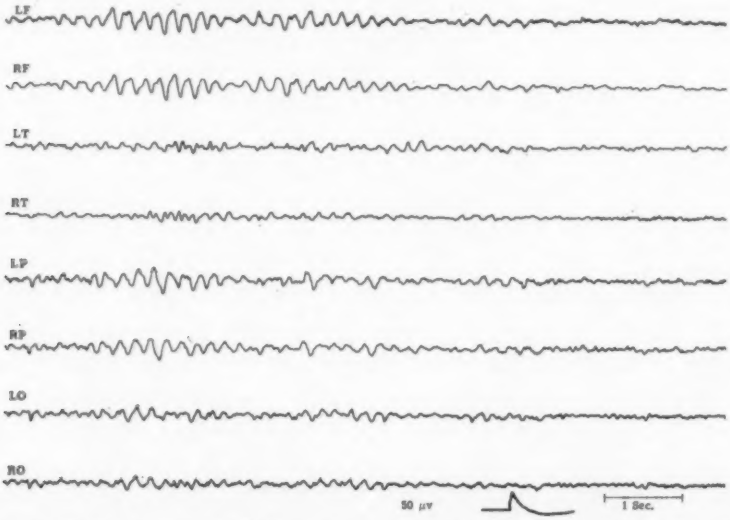


Fig. 11 (Krill and Stamps). Diffuse slow waves of five to seven per second frequency are noted in all leads.

ganic brain disorder, and to be rare in adult controls.[21] The patient with the diffuse frontal-parietal seizure record (Case 21) showed a pattern found in grand mal epilepsy. (One case omitted from this series because of a history of trauma had an identical seizure type of record.) This pattern was not noted in a series of 780 normal controls of all ages.[21]

In an analysis of these seven cases one notes that five patients had an onset of ocular symptoms before the age of 10 (Cases 6, 7, 11, 17, and 21), three had other members of the family with retinitis pigmentosa (Cases 6, 7, and 17), two had parents that were related (Cases 19 and 11), and three had associated findings (Cases 6, 7, and 19). The ocular findings, which are not shown in Table 1, varied greatly in this group.

The finding of a flat record in a 56-year-old woman (Case 24) is not unusual since Adams found flat records in 11 percent of 427 normals 40 to 69 years of age.[22]

In this series six records (19 percent) were interpreted in the category of low-voltage records. In a series of 1,000 normal controls, which included many younger individuals, Gibbs, Gibbs, and Lennox found this type of record in 11.6 percent of the records.[23] The incidence of this finding increases with age. In a recent analysis of 233 normal controls beyond the age of 29 years, Gibbs and Gibbs found this type of record in 15 percent of the patients with the incidence varying from 12 percent in the 30 to 39 age group to 35 percent beyond the age of 60 years.[21] In view of the ages of our six patients, (Cases 36, 37, 38, 40, 55, and 58) it is felt that our finding of 19 percent is not significant.

Our study revealed a lower percentage of abnormalities than the three previous studies of patients with retinitis pigmentosa.

François, Stefans, and DeRouck found 18 of 22 cases of tapetoretinal degenerations to be abnormal.[11] Included in this study were two cases of retinitis punctata albescens. The characteristic finding was a diffuse and polymorphic dysrhythmia of a generally low microvoltage. François concluded that the electroencephalogram changes were of great importance in the differential diagnosis of tapetoretinal degenerations.[24] Our interpretation of most of these recordings would have been that of low-voltage alpha waves or flat records to which we, as previously stated, attach little significance.

Streifler and Landau found 12 out of 25 cases with abnormal records, five of which were considered slight abnormalities, and seven of which deviated markedly from the norm.[12] They found no disturbances in alpha activity, no unusual reactions to "blocking stimuli," and no correlation between the impairment of visual function and the presence of electroencephalogram abnormalities. The most common abnormality noted was a pattern of bilateral symmetric and synchronous slow waves which usually appeared diffusely and became more manifest during and after hyperventilation. Our interpretation of some of these records may have differed from the above authors since large amplitude slow waves are often more prominent during and after hyperventilation[14] and, as indicated previously, the degree of this finding (the build-up) will vary with many circumstantial factors.[14, 25] In one case with a paroxysmal type of abnormality it was mentioned by the authors that the mother of the patient suffered from epilepsy. Since it is known that so-called "normal" relatives of epileptics can also show paroxysmal outbursts, this finding cannot be said to be related to retinitis pigmentosa. A study by Lennox, Gibbs, and Gibbs of 183 relatives of 94 patients with clinical epilepsy revealed 60 percent of abnormalities.[26]

In the study of tapetoretinal degenerations by Cordier, Dureux, and Barbier, 13 of 17 cases of retinitis pigmentosa studied were designated as having abnormal records.[10] Seven of these cases had paroxysmal disorders. The authors found that in all 10 of their cases with onset of symptoms at an age below five years and in all five of their

cases with definite simple recessive or sex-linked heredity there were abnormal electroencephalograms. Included in these 17 cases were one case of epilepsy with a paroxysmal disorder and four cases of oligophrenia. Oligophrenia is associated with a high percentage of paroxysmal disorders. Fois, Rosenberg, and Gibbs found 18 cases out of 19 studied with this diagnosis to be associated with seizure activity.[27]

In none of the studies, including the present, was a control group of secondary pigmentary degenerations related to bacterial and viral diseases studied. Since it is known that neurosyphilis can cause electroencephalographic abnormalities,[28] this condition would have to be excluded before diagnostic value could be ascribed to the electroencephalogram.

## Summary and Conclusions

An electroencephalographic study of 32 patients with retinitis pigmentosa disclosed seven abnormalities. All of the abnormalities were apparent primarily during sleep and drowsiness and could be considered diffuse in nature. These characteristics suggested subcortical disturbances.

No definite pattern could be ascribed to retinitis pigmentosa patients because of the diverse abnormalities described by this (four different patterns) and by previous studies. These variations may be related to a possible diversity of the group of diseases called retinitis pigmentosa.

No characteristic phenomena were noted in alpha blocking studies; hyperventilation, in 12 cases, was of no value in detecting additional abnormalities.

Previous studies reported a higher percentage of abnormalities than the present study. Differences in interpretation of the records and in the selection of patients probably account for this.

From this study it appears unlikely that the electroencephalogram is of any value in the differential diagnosis of pigmentary degenerations of the retina.

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# THE USE OF SUCCINYLCHOLINE IN OCULAR SURGERY

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Succinylcholine chloride is a relatively new, extremely short-acting, skeletal muscle relaxant; that is, following intravenous injection of small doses, there is onset of relaxation within 45 to 60 seconds, persisting for approximately three minutes, with complete recovery in almost every case within five minutes. Because of its rapid onset and the quick return of muscle tonus, it is possible to obtain a moment to moment control of the degree and duration of relaxation that is not possible with any other relaxant. For these reasons it has become very popular in anesthesia and is quite widely used. An editorial in *Anesthesiology*, in 1957, states that "the drug comes very close to being the ideal muscle relaxant."[7]

The advantages which it enjoys in general anesthesia are applicable to ocular surgery. However, several investigators have reported increases in intraocular pressure accompanying the injection of succinylcholine and the results of at least one study showing this have been widely discussed and have caused a number of ophthalmologists and anesthesiologists to distrust its use in ocular cases.

One of us serves on the staff of the state mental hospital where almost all surgery has to be done under general anesthesia because of the uncertainty of co-operation. A rule of the department requires all such patients to be intubated, and because of the ease with which succinylcholine can be used in such cases we found ourselves doing cataract surgery under general endotracheal anesthesia employing pentothal, succinylcholine, nitrous oxide and oxygen. Because of the absence of deleterious side-effects which could be attributed to the succinylcholine, it was decided to conduct a study of the intraocular pressure on these patients. In order to

increase the number of cases available for statistical purposes a concurrent study of the intraocular pressure was undertaken on general surgical patients who were intubated following pentothal and succinylcholine. The findings, results, and conclusions are the subject of this report.

Eighty-two general surgical cases were examined in sequence with no selectivity. All patients were given preoperative medication, consisting in most cases of morphine sulfate or Demerol and atropine or scopolamine in suitable dosage for age and weight. All patients were induced with intravenous sodium pentothal and were well oxygenated by mask under positive pressure. Initial tension was taken at this point. After thorough oxygenation a single injection of succinylcholine (40 mg.) was given intravenously. This is the average dose used to facilitate intubation in the average adult; slight variations were used in the very old or young or where size dictated.

Within 30 to 40 seconds in nearly all cases fasciculation of the muscles of the neck and shoulders was observed. These are used as an indication to the anesthesiologist that depolarization is taking place and that maximum relaxation is rapidly ensuing. A second tonometer reading was taken at one minute from the time of injection, following which intubation was accomplished and the patient again well oxygenated by positive pressure with the gas machine. Tonometer readings were then taken at two-minute intervals until a total of seven minutes had elapsed from the injection of the succinylcholine. All patients were observed for evidence of retraction of the globe.

Although no measurements with an exophthalmometer were made, no case was observed in which there was any apparent retraction. Rotation of the eyes upward is a frequent occurrence under light anesthesia of any sort and occurred in almost all cases of this series following the beginning of the pentothal injection but before the succinylcholine had been given. In no case was any additional rotation or change in position noted following the administration of the succinylcholine. As Table 1 shows, the tension in nearly all cases one minute after the succinylcholine was given was either equal to, or slightly less, than the initial tension.

Following intubation a definite rise was seen in almost all cases; this was of short duration and subsided within three to five minutes as the patient was gradually deepened in anesthesia and relaxation became more apparent. Although all these cases were done by an experienced anesthesiologist or anesthetist, a certain degree of "bucking or coughing on the tube" was manifested by most patients. This period coincided with the rise in tension.

According to Adler, "if the venous return from the head is blocked, the intraocular pressure rises enormously. By damming the return flow blood back into the eye, all the blood vessels dilate ad maximum and the intraocular pressure increases to the highest values found under pathological conditions."[1] In the normal individual, these changes can be brought about by the Val Salva maneuver which blocks the return of venous blood by increasing the intrathoracic pressure on the vena cava. The resistance of a patient to intubation can be compared with the Val Salva maneuver in which thoracic pressure is raised to or above 40 mm. Hg for at least eight seconds and it is felt that many patients undergoing intubation fulfill these conditions. In a few cases, prolonged coughing or tube resistance was noted to result in definite congestion of the conjunctiva and tearing. These few cases all showed prolonged increases in intraocular pressure and in general showed the highest rises observed in the series (Cases 6, 12, 20, 28, 30, 31, 36, and 41).

Seven patients in this series were not intubated but were given succinylcholine after pentothal induction. While representing only 8.5 percent of the cases, it is significant that no appreciable rise in tension was seen in any one of them and in two there was a defi-

nite drop in the measurement following the injection of succinylcholine.

In the series of 13 cataract cases (table 2), the tensions were found to conform fairly well with those of the general surgical cases. In only one case (9) was the tension significantly elevated after succinylcholine was given and this patient was noted to be coughing some prior to being intubated. In all other cases tension was equal to or lower than the initial tension. Following intubation, a rise was observed in all cases with a maximum rise of 16.5 mm. Hg in the right eye of Case 10. Again these elevations fell within five to seven minutes to well within normal limits. A retrobulbar injection of two-percent Xylocaine was administered in all cases and resulted in still lower tension in all but one case (6).

In three cases a retrobulbar injection of two-percent Xylocaine was administered prior to giving the succinylcholine and intubation. A rise was observed following intubation just as in the other cases, confirming the thought that a retrobulbar injection of two-percent Xylocaine is no protection against a rise in tension which is basically due to hemostasis.

In two of the 13 cataract cases there was vitreous loss. In one case (6) the tension was extremely low (7.0 to 10 mm. Hg.) The lens capsule seemed adherent to the vitreous face and loss of vitreous accompanied lens delivery. In the other case (10), there was bulging of the vitreous face as the lens delivered, and rupture with loss ensued. This patient's tension was 15.6 mm. Hg following the retrobulbar injection and massage, and it is doubtful that the succinylcholine contributed in any way to the accident.

All of the cataract cases received succinylcholine by intravenous drip throughout the procedure to facilitate relaxation and several of them received an additional injection of 20 mg. to facilitate extubation upon completion of the procedure. In no case was any untoward effect seen from this.

Seven squint cases were included in the series of general surgical cases. As stated above, no abnormal rotation was seen, and no difficulty was experienced in carrying out the desired surgery.

One enucleation was done in a young man with absolute glaucoma. All muscles except the medial rectus were detached from the globe and 40 mg. of succinylcholine were given. No rotation or movement of the globe was observed for a five-minute period.

The opportunity was presented to check the intraocular pressure on one patient who was bronchoscoped and intubated awake. His initial tension was: O.D., 15; O.S., 15.6 mm. Hg. He was given a pharyngeal spray and a transtracheal injection of cocaine after which he was bronchoscoped. Tension immediately after bronchoscopy was: O.D., 20.1; O.S., 17 mm. Hg. Following this an endotracheal tube was passed which provoked some coughing. Tension rose to: O.D., 23.8; O.S., 21.9 mm. Hg. Intravenous pentothal and succinylcholine drip were instituted for anesthesia and three minutes later the tension was: O.D., 9.1; O.S., 7.5 mm. Hg.

Hofmann and Holzer were the first to report that succinylcholine had an adverse effect on intraocular pressure.[3] They published a report in 1953 stating that succinylcholine caused an increase in intraocular pressure. Their experimental work was done on conscious patients who reported a feeling of pressure in the orbits, vertigo and diplopia. They also found increases in pressure in patients under anesthesia.

In 1955, Lincoff[6] and his co-workers published a report in which ocular tensions were measured on electroshock patients receiving very small doses of pentothal with succinylcholine. They found increases in intraocular pressure in practically all cases. Other experimental data reported by them indicated that the intraocular pressure rise seemed to be due to contracture of the extraocular muscles and their conclusions were that succinylcholine should be used with caution in intraocular surgery.

TABLE 1

OBSERVED TENSIONS (MM. HG, SCHIØTZ) ON PATIENTS UNDER GENERAL ANESTHESIA

| Patient | Initial Tension | Tension after Succinylcholine | Intubated & $O_2$ Tension—3 Min. | Tension—5 Min. | Tension—7 Min. | Patient | Initial Tension | Tension after Succinylcholine | Intubated & $O_2$ Tension—3 Min. | Tension—5 Min. | Tension—7 Min. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 14.3 | 18.5 | 42.1 | 30.4 | 17.0 | 21 | 18.5 | 18.5 | 25.8 | 25.8 | 25.8 |
| | 13.1 | 15.6 | 33.0 | 23.8 | 13.1 | | 20.1 | 18.5 | 25.8 | 25.8 | 21.9 |
| 2 | 15.6 | 18.5 | 35.8 | 30.4 | 25.8 | 22 | 13.1 | 13.1 | 15.6 | 13.1 | 12.0 |
| | 18.5 | 18.5 | 30.4 | 25.8 | 21.9 | | 13.1 | 13.1 | 13.1 | 10.9 | 9.1 |
| 3 | 18.5 | 20.1 | 30.4 | 23.8 | 13.1 | 23 | 14.3 | 10.9 | 21.9 | 18.5 | 20.1 |
| | 20.1 | 18.5 | 21.9 | 17.0 | 14.3 | | 14.3 | 10.9 | 23.8 | 20.1 | 20.1 |
| 4 | 15.6 | 15.6 | 14.3 | 15.6 | 14.3 | 24 | 13.1 | 10.9 | 35.8 | 25.8 | 25.8 |
| | 13.1 | 14.3 | 13.1 | 15.6 | 13.1 | | 10.0 | 10.1 | 25.8 | 21.9 | 21.9 |
| 5 | 18.5 | 18.5 | 35.8 | 30.4 | 21.9 | 25 | 12.0 | 15.6 | 25.8 | 21.9 | 18.5 |
| | 21.9 | 20.1 | 35.8 | 30.4 | 21.9 | | 12.0 | 15.6 | 25.8 | 21.9 | 20.1 |
| 6* | 15.6 | 30.4 | 25.8 | 21.9 | 17.0 | 26 | 18.5 | 18.5 | 33.0 | 21.9 | 18.5 |
| | 14.3 | 30.4 | 25.8 | 21.9 | 17.0 | | 20.1 | 18.5 | 30.4 | 18.5 | 13.1 |
| 7 | 12.0 | 13.1 | 30.4 | 30.4 | 25.8 | 27 | 17.0 | 13.1 | 25.8 | 20.1 | 18.5 |
| | 15.6 | 14.3 | 30.4 | 30.4 | 25.8 | | 15.6 | 13.1 | 25.8 | 20.1 | 20.1 |
| 8 | 10.9 | 10.9 | 14.3 | 13.1 | 7.5 | 28* | 15.6 | 18.5 | 42.1 | 33.0 | 25.8 |
| | 9.1 | 10.9 | 15.6 | 12.0 | 9.1 | | 15.6 | 13.1 | 35.8 | 25.8 | 18.5 |
| 9 | 15.6 | 15.6 | 18.5 | 25.8 | 15.6 | 29 | 18.5 | 21.9 | 25.8 | 23.8 | 21.9 |
| | 13.1 | 15.6 | 18.5 | 25.8 | 15.6 | | 21.9 | 21.9 | 25.8 | 25.8 | 21.9 |
| 10 | 13.1 | 14.3 | 25.8 | 18.5 | 13.1 | 30* | 13.1 | 14.3 | 35.8 | 25.8 | 18.5 |
| | 14.3 | 13.1 | 25.8 | 21.9 | 15.6 | | 13.1 | 14.3 | 42.1 | 25.8 | 20.1 |
| 11 | 10.9 | | 20.1 | 18.5 | 15.6 | 31* | 17.0 | 18.5 | 35.8 | 30.4 | 25.8 |
| | 13.1 | | 21.9 | 20.1 | 15.6 | | 21.9 | 25.8 | 42.1 | 35.8 | 35.8 |
| 12* | 18.5 | 25.8 | 28.0 | 30.4 | 23.8 | 32 | 12.2 | 10.9 | 15.6 | 13.1 | 10.9 |
| | 20.1 | 25.8 | 30.4 | 25.8 | 21.9 | | 14.6 | 13.1 | 15.6 | 10.9 | 10.9 |
| 13 | 10.9 | 15.6 | 25.8 | 21.9 | 18.5 | 33 | 18.5 | 20.1 | 25.8 | 18.5 | 15.6 |
| | 13.1 | 17.0 | 28.0 | 23.8 | 21.9 | | 15.6 | 17.0 | 25.8 | 18.5 | 15.6 |
| 14 | 13.1 | 13.1 | 21.9 | 21.9 | 17.0 | 34 | 15.6 | 15.6 | 15.6 | 12.0 | 12.0 |
| | 10.9 | 10.9 | 21.9 | 21.1 | 15.6 | | 14.3 | 13.1 | 13.1 | 10.9 | 15.6 |
| 15 | 15.6 | 14.3 | 30.4 | 25.8 | 17.0 | 35 | 9.1 | 18.5 | 25.8 | 15.6 | 15.6 |
| | 10.9 | 12.0 | 21.9 | 21.1 | 13.1 | | 10.9 | 18.5 | 25.8 | 18.5 | 13.1 |
| 16 | 13.1 | 10.9 | 20.1 | 18.5 | 14.3 | 36* | 10.9 | 18.5 | 35.8 | 23.8 | 30.4 |
| | 10.9 | 10.9 | 18.5 | 15.6 | 13.1 | | 10.9 | 18.5 | 30.4 | 18.5 | 35.8 |
| 17 | 15.6 | 13.1 | 20.1 | 17.0 | 10.9 | 37 | 13.1 | 14.3 | 25.8 | 20.1 | 12.0 |
| | 18.5 | 17.0 | 21.9 | 15.6 | 13.1 | | 17.0 | 15.6 | 18.5 | 18.5 | 12.0 |
| 18 | 13.1 | 12.0 | 15.6 | 14.3 | 10.9 | 38 | 13.1 | 10.9 | 21.9 | 18.5 | |
| | 13.1 | 12.0 | 15.6 | 14.3 | 10.9 | | 10.9 | 10.9 | 21.9 | 20.1 | |
| 19 | 15.6 | 20.1 | 35.8 | 30.4 | 23.8 | 39 | 14.3 | 6.8 | 28.0 | 35.8 | 25.8 |
| | 17.0 | 21.9 | 35.8 | 30.4 | 23.8 | | 18.5 | 9.1 | 25.8 | 35.8 | 18.5 |
| 20* | 14.3 | 13.1 | difficult | 35.8 | 28.0 | 40 | 17.0 | 15.6 | 35.8 | 23.8 | 15.6 |
| | 14.3 | 13.1 | intubation | 35.8 | 28.0 | | 18.5 | 18.5 | 33.8 | 28.0 | 17.0 |

* Congestion of conjunctiva and tearing.

TABLE 1 (*Continued*)

| Patient | Initial Tension | Tension after Succinylcholine | Intubated & $O_2$ Tension—3 Min. | Tension—5 Min. | Tension—7 Min. | Patient | Initial Tension | Tension after Succinylcholine | Intubated & $O_2$ Tension—3 Min. | Tension—5 Min. | Tension—7 Min. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 41* | 15.6 | 15.6 | 42.1 | 42.1 | 25.8 | 62 | 14.3 | 15.6 | 14.3 | 13.1 | 13.1 |
| | 15.6 | 15.6 | 42.1 | 49.8 | 25.8 | | 15.6 | 17.0 | 15.6 | 14.3 | 14.3 |
| 42 | 13.1 | 17.0 | 15.6 | 12.0 | 10.0 | 63 | 10.9 | 10.9 | 10.9 | 10.0 | 10.0 |
| | 13.1 | 17.0 | 15.6 | 10.0 | 7.5 | | 10.9 | 13.1 | 9.1 | 8.3 | 8.3 |
| 43 | 10.9 | 9.1 | 21.9 | 18.5 | 15.6 | 64 | 8.3 | 10.9 | 9.1 | 10.0 | 12.0 |
| | 13.1 | 13.1 | 21.9 | 18.5 | 14.3 | | 4.1 | 4.1 | 5.0 | 5.0 | 7.5 |
| 44 | 17.0 | 18.5 | 23.8 | 20.1 | 20.9 | 65 | 17.0 | 18.5 | 18.5 | 18.5 | 17.0 |
| | 18.5 | 21.9 | 25.8 | 21.9 | 20.9 | | 20.1 | 18.5 | 17.0 | 18.5 | 18.5 |
| 45 | 14.3 | 12.0 | 18.5 | 15.6 | 13.1 | 66 | 17.0 | 14.3 | 15.6 | 15.6 | 15.6 |
| | 8.3 | 10.0 | 14.3 | 12.0 | 10.0 | | 18.5 | 15.6 | 15.6 | 15.6 | 15.6 |
| 46 | 12.0 | 15.6 | 25.8 | 21.9 | 20.1 | 67 | 23.8 | 25.8 | 21.9 | 20.1 | 20.1 |
| | 10.9 | 12.0 | 25.8 | 18.5 | 17.0 | | 20.1 | 21.9 | 18.5 | 18.5 | 18.5 |
| 47 | 15.6 | 21.9 | 35.8 | 28.0 | 23.8 | 68 | 13.1 | 13.1 | 12.0 | 13.1 | 10.0 |
| | 15.6 | 21.9 | 35.8 | 28.0 | 18.5 | | 13.1 | 13.1 | 12.0 | 13.1 | 10.0 |
| 48 | 15.6 | 13.1 | 18.5 | 18.5 | 15.6 | 69‡ | 15.6 | 15.6 | 14.3 | 14.3 | 14.3 |
| | 15.6 | 12.0 | 17.0 | 18.5 | 15.6 | | 18.5 | 18.5 | 18.5 | 17.0 | 17.0 |
| 49 | 10.9 | 21.0 | 30.4 | 28.0 | 18.5 | 70‡ | 18.5 | 15.6 | 13.1 | 13.1 | 10.9 |
| | 10.9 | 18.5 | 30.4 | 28.0 | 15.6 | | 21.9 | 13.1 | 13.1 | 10.9 | 9.1 |
| 50 | 14.3 | 21.9 | 25.8 | 18.5 | 15.6 | 71‡ | 18.5 | 13.1 | 10.9 | 13.1 | 13.1 |
| | 15.6 | 21.9 | 21.9 | 17.0 | 14.3 | | 18.5 | 15.6 | 13.1 | 13.1 | 13.1 |
| 51 | 9.1 | 9.1 | 13.1 | 15.6 | 14.3 | 72† | 15.6 | 21.9 | 33.0 | 18.5 | 18.5 |
| | 7.5 | 7.5 | 13.1 | 15.6 | 13.1 | | 18.5 | 23.8 | 35.8 | 25.8 | 18.5 |
| 52 | 9.1 | 15.6 | 21.9 | 25.8 | 21.9 | 73† | 15.6 | 18.5 | 17.0 | 17.0 | 15.6 |
| | 10.9 | 18.5 | 25.8 | 21.9 | 18.5 | | 13.1 | 15.6 | 14.3 | 13.1 | 13.1 |
| 53 | 10.9 | 18.5 | 21.9 | 18.5 | 18.5 | 74† | 18.5 | 18.5 | 15.6 | 15.6 | 15.6 |
| | 13.1 | 15.6 | 21.9 | 18.5 | 15.6 | | 15.6 | 17.0 | 15.6 | 13.1 | 13.1 |
| 54 | 13.1 | 13.1 | 13.1 | 14.3 | 14.3 | 75 | 18.5 | 18.5 | 25.8 | 25.8 | 25.8 |
| | 10.9 | 9.1 | 9.1 | 9.1 | 9.1 | | 18.5 | 18.5 | 35.8 | 30.4 | 25.8 |
| 55 | 17.0 | 18.5 | 18.5 | 18.5 | 17.0 | 76† | 18.5 | 14.3 | 21.9 | | 13.1 |
| | 18.5 | 18.5 | 18.5 | 15.6 | 17.0 | | 18.5 | 14.3 | 20.1 | | 10.9 |
| 56 | 15.6 | 15.6 | 15.6 | 18.5 | 18.5 | 77† | 15.6 | 14.3 | 25.8 | | 21.9 |
| | 15.6 | 13.1 | 14.3 | 18.5 | 18·5 | | 15.6 | 13.1 | 25.8 | | 21.9 |
| 57 | 21.9 | 17.0 | 15.6 | 15.6 | 15.6 | 78† | 9.1 | 13.1 | 10.9 | 10.9 | 10.0 |
| | 25.8 | 20.1 | 20.1 | 18.5 | 18.5 | | 9.1 | 10.0 | 10.9 | 10.0 | 9.1 |
| 58 | 13.1 | 10.9 | 12.0 | 13.1 | 10.9 | 79† | 18.5 | 25.8 | 35.8 | 28.0 | 23.8 |
| | 15.6 | 14.3 | 15.6 | 14.3 | 13.1 | | 18.5 | 25.8 | 35.8 | 28.0 | 23.8 |
| 59 | 5.0 | 13.1 | 10.9 | 7.5 | 6.2 | 80‡ | 10.9 | 13.1 | 13.1 | 13.1 | 13.1 |
| | 6.8 | 15.6 | 9.1 | 6.8 | 5.0 | | 9.1 | 9.1 | 9.1 | 8.3 | 8.3 |
| 60 | 18.6 | 18.5 | 18.5 | 18.5 | 18.5 | 81‡ | 10.9 | 10.9 | 10.9 | 10.9 | 10.9 |
| | 17.0 | 17.0 | 14.3 | 17.0 | 17.0 | | 10.9 | 10.9 | 13.1 | 13.1 | 10.9 |
| 61‡ | 9.1 | 10.9 | 9.1 | 7.5 | 6.8 | 82‡ | 18.5 | 20.1 | 18.5 | 13.1 | 10.9 |
| | 9.1 | 9.1 | 9.1 | 7.5 | 6.8 | | 12.0 | 15.6 | 13.1 | 10.9 | 10.9 |

† Squint.
‡ Not intubated

TABLE 2

CATARACT CASES

| Case No. | Patient | Age (yr.) | Initial Tension (mm.Hg) | Tension One Minute after Succinylcholine (mm.Hg) | Intubation & Aeration Tension (mm.Hg) | Tension Five Minutes (mm.Hg) | Tension Seven Minutes (mm.Hg) | Retrobulbar Injection Xylocaine & Massage | Surgical Procedure | Condition of Vitreous | Tension Unoperated Eye at Completion (mm.Hg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | J. H. | 90 | O.D.: 17.0<br>O.S.: 13.1 | O.D.: 15.6<br>O.S.: 10.9 | O.D.: 21.9<br>O.S.: 18.5 | O.D.: 21.9<br>O.S.: 17.0 | O.D.: 21.9<br>O.S.: 17.0 | †O.D.: 13.1<br>O.S.: 18.5 | Extracap. c̄ iridectomy | Scaphoid—no loss | O.S.: 21.9 |
| 2 | L. T. | 76 | O.D.: 18.5<br>O.S.: 10.9 | O.D.: 18.5<br>O.S.: 7.5 | | O.D.: 21.9<br>O.S.: 10.9 | O.D.: 21.9<br>O.S.: 10.9 | †O.D.: 18.5<br>O.S.: 10.9 | Intracap. c̄ peripheral iridectomy | Scaphoid—no loss | O.S.: 15.8 |
| 3 | J. H. | 90 | O.D.: 23.5<br>O.S.: 23.5 | O.D.: 23.5<br>O.S.: 23.5 | | O.D.: 21.9<br>O.S.: 21.9 | O.D.: 21.9<br>O.S.: 21.9 | O.D.: 21.9<br>†O.S.: 15.6 | Intracap. c̄ iridectomy | Scaphoid—no loss | O.D.: 20.1 |
| 4 | J. W. | 61 | O.D.: 14.6<br>O.S.: 14.6 | O.D.: 12.2<br>O.S.: 10.2 | O.D.: 20.6<br>O.S.: 18.9 | O.D.: 17.3<br>O.S.: 15.9 | O.D.: 15.9<br>O.S.: 15.9 | †O.D.: 14.6<br>†O.S.: 15.9 | Intracap. c̄ iridectomy | Scaphoid—no loss | O.S.: 15.9 |
| 5 | J. W. | 61 | O.D.: 28.5<br>O.S.: 35.8 | O.D.: 23.5<br>O.S.: 30.5 | O.D.: 30.4<br>O.S.: 35.8 | O.D.: 30.4<br>O.S.: 33.0 | O.D.: 28.0<br>O.S.: 30.4 | O.D.: 28.0<br>†O.S.: 25.8 | Intracap. c̄ iridectomy morgagian lens | Flat—no loss | O.D.: 21.5 |
| 6 | E. H. | 59 | O.D.: 4.1<br>O.S.: 9.1 | O.D.: 4.1<br>O.S.: 8.3 | | O.D.: 4.1<br>O.S.: 7.5 | O.D.: 4.1<br>O.S.: 7.5 | O.D.: 4.1<br>†O.S.: 10.0 | Hypermature lens Intracap. c̄ iridectomy | Bulge Loss of fluid vitreous | O.D.: 4.1 |
| 7 | L. T. | 76 | O.D.: 13.1<br>O.S.: 17.0 | O.D.: 14.3<br>O.S.: 17.0 | | O.D.: 15.6<br>O.S.: 21.9 | O.D.: 15.6<br>O.S.: 20.1 | O.D.: 15.6<br>†O.S.: 13.1 | Intracap. c̄ peripheral iridectomy | Scaphoid—no loss | O.D.: 21.9 |
| 8 | N. S. | | O.D.: 10.9<br>O.S.: 7.5 | O.D.: 10.9<br>O.S.: 6.2 | O.D.: 17.5<br>O.S.: 7.5 | | O.D.: 10.9<br>O.S.: 5.0 | †O.D.: 7.5<br>O.S.: 4.1 | Intracap. c̄ peripheral iridectomy | Scaphoid—no loss | O.S.: 15.0 |
| 9 | M. M. | 74 | O.D.: 10.9<br>O.S.: 7.5 | O.D.: 18.5*<br>O.S.: 13.1 | O.D.: 21.9<br>O.S.: 18.5 | O.D.: 15.6<br>O.S.: 14.3 | | †O.D.: 9.1<br>O.S.: 10.9 | Intracap. c̄ iridectomy | Scaphoid—no loss | O.S.: 9.1 |
| 10 | F. T. | | O.D.: 13.8<br>O.S.: 15.6 | O.D.: 18.5<br>O.S.: 18.5 | O.D.: 35.8<br>O.S.: 25.8 | O.D.: 33.0<br>O.S.: 21.9 | O.D.: 21.9<br>O.S.: 21.9 | †O.D.: 15.6<br>O.S.: 15.6 | Intracap. c̄ iridectomy | Fluid vitreous lost c̄ lens delivery | O.S.: 25.8 |
| 11 | J. U. | 75 | O.D.: 13.1<br>O.S.: 15.6 | O.D.: 13.1<br>O.S.: 18.5 | O.D.: 25.8<br>O.S.: 33.0 | O.D.: 21.9<br>O.S.: 28.0 | O.D.: 18.5<br>O.S.: 25.8 | | Intracap. c̄ peripheral iridectomy | Scaphoid—no loss | O.S.: 13.1 |
| 12 | M. M. | 74 | O.D.: 12.0<br>O.S.: 7.5 | O.D.: 12.0<br>O.S.: 8.3 | O.D.: 21.9<br>O.S.: 15.6 | O.D.: 21.9<br>O.S.: 14.3 | O.D.: 18.5<br>O.S.: 14.3 | | Intracap. c̄ peripheral iridectomy | Scaphoid—no loss | O.D.: 18.5 |
| 13 | N. S. | | O.D.: 10.9<br>O.S.: 10.9 | O.D.: 10.9<br>O.S.: 15.6 | O.D.: 21.9<br>O.S.: 18.6 | O.D.: 13.1<br>O.S.: 15.6 | O.D.: 13.1<br>O.S.: 14.3 | O.D.: 10.9<br>O.S.: 10.9 | Intracap. c̄ peripheral iridectomy | Scaphoid—no loss | O.D.: 10.0 |

* Patient coughing prior to intubation.

Other writers reported cases of vitreous loss where succinylcholine was used and concluded that it was probably contraindicated in any ocular surgery because of the finding of Lincoff that the eye tended to rotate away from a severed muscle.[2] This left the situation somewhat confused as to exactly what use could be made of succinylcholine in ocular surgery.

In 1957, Lincoff published a supplemental report which confirmed the mechanism of the increase in pressure to be contracture of the extraocular muscles.[5] This was simultaneously confirmed by Macri and Grimes.[6] Lincoff, apparently based on direct communications with several surgeons, stated that under "deeper anesthesia" succinylcholine seemed to have no effect on intraocular pressure. We feel that our results substantiate his statement.

The rises in pressure shown in our cases are attributed to intubation and the resultant increased intrathoracic pressure with its direct effect on the vascular bed of the eye. These rises were all of short duration and in the series of intraocular cases had no deleterious effect on the procedure. Contrary to previous reports, no manifestations of contracture of the extraocular muscles such as enophthalmos or rotation of the globe were observed in any case of this series.

The use of a muscle relaxant as an adjunct to local anesthesia for ocular surgery has been advocated by Kirby and is discussed at length in his last book, *The Advanced Surgery of Cataract*.[4] Dr. Kirby limited his use to curare because curare exerts a specific descending type of paralysis in which the lid and extraocular muscles are first affected. By giving minimal doses slowly he found that relaxation of the globe could be enhanced in the otherwise tense or spastic type patient. He warns of the dangers inherent in such a potent drug and of precautions necessary in every case where it is used.

The mechanism of action of succinylcholine is different from that of curare and succinylcholine does not show the selectivity which is seen with curare. All skeletal muscle seems to be simultaneously affected and because of its rapid onset, respiratory depression and ensuing respiratory paralysis accompany the other early skeletal muscle relaxation.

The administration of a paralyzing drug to the conscious patient is a terrifying experience to the patient because of the feeling of asphyxia. There is an early increase in intrathoracic pressure because of inability to expand the chest. This gives a feeling of weight in the chest, leads to partial obstruction of the great veins, with resultant increases in venous pressure in the head and extremities, and probably accounts for the feeling of fullness and pressure in the orbits experienced by the conscious volunteers in Hofmann's and Holzer's experiments. Further work must be done to define the role of partial anoxia in these cases.

Succinylcholine should not be given to the conscious patient. It is contrary to good anesthesia principles to do so and there is no reason to make an exception of ocular cases. In the occasional case where such an agent is necessary it would appear that curare is the drug of choice, but it is to be used only after precautions are taken for the handling of any respiration eventuality which may arise.

## Conclusions

Succinylcholine has many advantages as a muscle relaxant and these are applicable to ocular cases under general anesthesia. We do not feel that it is contraindicated in such cases if it is used according to accepted techniques. Certainly there is no contraindication for its use in extraocular procedures.

The specific reason for its different effect on the intraocular pressure in the conscious patient as compared to the unconscious or anesthetized has not been defined, but we feel that the role of anoxia and the resultant venous blockage is a significant one. Intravenous drip of succinylcholine during intraocular procedures may be used safely as

long as an adequate level of anesthesia is maintained. Succinylcholine should not be given to the conscious patient and therefore should not be used as an adjunct to ocular surgery under local anesthesia.

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# THE ORIGIN OF THE AQUEOUS HUMOR*

## And the Secretory Activity of the Epithelium of the Ciliary Body

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The origin of the aqueous humor is a problem in which, since Mery (1707), many investigators have been interested. Its formation plays an important role in the unsolved question of the etiology of glaucoma. The special histologic pattern of the ciliary body, with abundant plicae lined by epithelium and lying on a connective vascular network, which increases to a maximum its functional surface, has directed the investigations to (1) the epithelium, and (2) the blood. Until now, however, evidence has not been found convincing and present data are often irreconcilable. Because of the apparent absence of secretion in the clear cells of the ciliary epithelium, the secretory theory first gave way to the physicochemical theory, and more recently to the modified secretion-diffusion hypotheis.

The study of the histologic structure of the ciliary body by means of silver impregnation methods (Achúcarro, Río Hortega) enabled me to observe cellular forms suggestive of a direct connection between the lining epithelium and the formation of the aqueous humor.

Three hypothesis have been developed to explain the formation of the aqueous humor: (1) the ciliary body is a gland (the secretory theory); (2) the filtration, and (3) the dialyzation theories (these two involve the vascular system).

### The Secretory Theory

The earliest investigators considered the fluid of the anterior chamber of the eye as a secretion of the ciliary body (Mery, 1707, Haller, 1757, and Zinn, 1775). Zinn observed that in the embryonic eye, before the perforation of the pupillary membrane of Wachendorf, that there was no liquid or only a few drops in the anterior chamber. His very words were "maximam partem humoris aquei ex willia arteriosis processum ciliarum provenire." In agreement with this was Vetch (1820) and later on Boucheron (1883) divided the ciliary body into an anterior part, formed by the posterior epithelium of the iris and the extremity of the processes, and a posterior part which formed the base;

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the anterior part would secrete the aqueous humor, the posterior the vitreous body.

Nicati (1890) conceived that the aqueous was a product elaborated by a gland. He named this gland the uvea and believed it was formed by the ciliary epithelium, the iris, and the papillary corium. According to Nicati the mechanism would be a real secretion by the glandular epithelium that extends from the ora serrata to the root of the iris. There would also be two kinds of aqueous.

Treacher Collins (1891) believed that the secretory activity was the function of certain excrescences of the pigmentary layer that passes from the retina to the ciliary body. He classified this body as the ciliary gland. Griffith (1894) believed, however, that the hypothetic ciliary glands regulated pigments.

This brief review points out the inaccuracy of the anatomic data used as the basis for the secretory theory of aqueous formation. Nevertheless this hypothesis lasted for years and was sustained by new arguments. Panas and Rochon-Duvigneaud (1894) accepted it enthusiastically.

Mawas (1910) made interesting observations on the ciliary epithelium. He saw in the layer of clear cells a variety of shapes, places and staining properties of the nuclei and believed that these nuclei belonged to very active glandular cells. However, the protoplasm of these cells would show fresh, refringent granules with the characteristics of granules of secretion. These granules could be dissolved by several fixing agents (acetic acid, Bouin and Zenker fluids); they had the shape of mitochondria and lipoid vesicles with the method of Regaud. Mawas also believed that the epithelium of clear cells had a passive role as a wall between the aqueous and the blood.

Since these investigations, great importance has been given to the mitochondria as the basis of the glandular theory of the ciliary body. Seidel (1918-1920), Carrere (1923), Albrich (1923), Stella (1926), D'Amico (1928), Farina (1928) and Rotschin (1929) insisted on this theory and on its possible significance in the activity of the ciliary body, which was defined as an ocular gland. Seidel observed drops and vesicles in the ciliary epithelium of the cat, the rabbit, and the goose, especially on the surface of the cells. He saw that they were increased by pilocarpine. Carrere reported that these vesicles increased when the aqueous was removed.

Schmelzer (1925) and Schall (1925) claimed to have demonstrated the high content of oxidases of the ciliary epithelium. But, if a strongly positive oxidase reaction means a high oxygen uptake, it does not prove the glandular function of the tissue. Fisher (1929) reported the same kind of oxidizing properties and said that the iris has a high reducing power.

The secretory theory has been defended by theoretic arguments but not by the observation of positive facts which would confirm or disprove the existence of the secretion attributed to the ciliary epithelium. Thus, when some authors discuss the filtration or the dialyzation theories they tend to consider the postcorneal fluid as a product elaborated by the cells. Angelucci (1904), Hill (1913), and Flack (1918) made biochemical and physiologic observation; Seidel (1920) found a too low intraocular blood pressure to permit any filtration and held to the secretory hypothesis on the basis of the effects of such drugs as eserine and atropine that stimulate or impair glandular secretions affecting nervous mechanisms.

Many other experiments seemed to confirm the secretory theory of the aqueous. Those of Friedenwald and Pierce (1932) who found the unilateral permeability of the epithelium; those of Adler (1933) who could determine a higher content of urea in the plasma than in the aqueous; the studies of Robertson (1937, 1938, 1939) who reported that the low hydrostatic pressure that exists in the capillaries is unfavorable to filtration; Friedenwald and Stiehler (1938) who inclined to the secretory theory because the fixation of basic aniline stains on the

ciliary epithelium is an impairment to filtration or dialysis; Botazzi and Sturchio (1905) and Scalinci (1907) who studied the conductivity and cryoscopic properties of the aqueous and, with many other investigators, contributed to the secretory hypothesis.

### The filtration theory

This theory grew out of the experiments of Leber (1885-1903), who passed a catheter through the pupils after the cornea was removed and observed the flow of fluid drop after drop from the cannula. This fluid was considered the result of a simple filtration of plasma through the ciliary body. Leber intended to control the flow by removing the tissues in which the aqueous could be secreted; he failed in his attempts. Deutschmann (1880), more lucky, proved by means of the same experiment that no aqueous was formed under these conditions, a result quite opposite to that expected.

To find the source of the aqueous, Ehrlich (1880) injected fluorescein subcutaneously and extracted the fluid from the eye when the yellowish color was apparent. Thus, the stain, mixed with blood, had entered the aqueous. Identical results were obtained by Scholer and Uhthoff (1882), Panas (1887), Parsons (1903), and Henderson and Starling (1904).

According to the filtration theory, the capillaries of the ciliary body would be permeable to crystalloids but not to colloids of the plasma. Consequently the filtered fluid would be devoid of proteins and the crystalloids and other substances would be in the same proportion as in the blood. But this argument is not yet proved; on the contrary, it has been reported that the aqueous is richer in chlorides than the plasma. To explain this higher content of chlorides Leber supposed that there was a loss of water through the cornea and thus imagined a new hypothesis.

### The dialyzation theory

The imperfect data supporting the existence of a ciliary gland and a secretory property of the ciliary body, together with the arguments against the filtration theory have given way to a newer hypothesis held by Magitot (1917). This theory says that the aqueous is a dialysate of plasma. As we know dialyzation implies the existence of a membrane permeable to crystalloids but not to colloids and an equilibrium between the fluids at each side of it (plasma and the aqueous in this case).

Further research performed by Meesmann (1924-1925), Baurmann (1924-1925), and Duke-Elder (1927) confirmed Magitot's theory. This theory is based on the quantitative analysis of the chemical components of the blood and of the aqueous and, also, on the study of the osmotic and hydrostatic pressure of both fluids. Theoretically, there would exist a chemical, osmotic, and hydrostatic equilibrium between the fluids. Several authors have opposed the dialyzation hypothesis on the basis of microchemical and physical arguments. One of them, Adler (1933) remarked the difference that exists between the concentration of urea in the blood and in the aqueous.

Robertson (1937, 1938, 1939) proved that a significant difference existed between intraocular pressure and blood pressure. He argued that the formation of the aqueous is not the result of a simple physical phenomenon, neither is it the consequence of dialysis, because of the following several reasons: urea and glycose concentrations are lower in the aqueous than in the blood; ascorbic acid values are higher; there is hyaluronic acid in the aqueous and it does not appear in the blood (Mayer and Palmer, 1936); osmotic pressure is of no value to differentiate between a dialysate and a secretion, because both fluids will be isotonic with the blood; finally, no physicochemical equilibrium exists between the fluids on either side of the epithelium. Robertson concludes that the aqueous is a secretion. However, as this has not yet been demonstrated, it gives way to such arguments as those that

Duke-Elder uses to support the Magitot approach.

It is not my purpose to discuss critically all the literature about these three hypotheses but several details of the structure of the ciliary epithelium should be mentioned. In addition to vesicles and granules, it is known that the ciliary body has a selective permeability to basic and acid anilines which can pass from the blood to the aqueous and vice versa; the epithelium is also metabollically different from the stroma because it contains a respiratory enzyme not demonstrated in the stroma.

Henderson (1914) also remarked, as a barrier to filtration or dialyzation, the double layer of epithelial cells that cover the ciliary body and the posterior part of the iris; this barrier is evident in the iris processes, pointing to the impermeability of the pigment layer of the iris to dialyzation. This argument leads to the belief that the aqueous penetrates the anterior chamber only because of the activity of the ciliary epithelium. Henderson agrees with the secretory theory and thinks that the "hypothetical glands" which produce the intraocular fluid must exist within the ciliary body.

Here, again, the secretory theory can only be supported by subjective ideas and not by experimental proof. The definite histologic evidence will be the demonstration of granules in the epithelial cells related to the granules of zimogen of the endocrine and exocrine glands, an evidence not yet reported.

The discussion of the different theories might go on and on, since definite evidence has not yet been found. In the meantime any contribution to clarify the problem is useful and so, in this study, data to support the secretory theory will be reported.

## Material and Methods

Materials from man, dogs, and rabbits were obtained under appropriate conditions and fixed in 10-percent formalin. The methods of Achúcarro and Río Hortega, especially designed to study the granules, were used. As the pigmentation of the ciliary body hinders study of the fine structure of the epithelial cells of both upper and lower layers, the melanin pigment was removed by the method of Río Hortega: the sections were covered with distilled water and sodium perborate. The dish was covered and left at room temperature or in an oven at 30°C. to 35°C. until the sections were decolored or became a pale yellow. Then they were washed and stained. Decoloration is based on the continuous loss of oxygen by the tissue and is complete after 24 hours.

The silver carbonate method of Río Hortega and its modifications were used for staining. The modification of Río Hortega's technique to Achúcarro's tannin method, suitable for staining cytoplasmic granules, was also used. This method takes advantage of the mordant property of the tannin in saturated solution and of the staining effect of Bielschowsky's silver method and is the only modification that does not require reduction with formalin. Certainly uniformity in the stainings was not obtained because the tenuousness of the ciliary body hastens the loosening of the mordant before the silver staining has begun and so this staining is less intense or lacks selectivity. However, in many cases the cellular granules could be well demonstrated, as is shown in the microphotographs.

## Cytologic study

The cytologic pattern of the ciliary region, from the ora serrata to the root of the iris, is well known and need not be described. All authors recognize the existence of a connective vascular network, rich in elastic fibers and provided with pigmentary elements, and a cellular layer which continues directly with the retina (pars ciliaris retinae). This is formed by a double layer of epithelial cells, one of them pigmented and dark colored and the other unpigmented and clear (fig. 1). The first layer is a prolongation of the pigmented layer of the

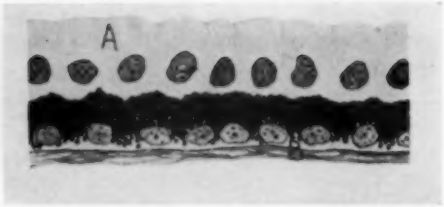


Fig. 1 (Sverdlick). Normal section of ciliary epithelium, showing two cellular layers, (A) superficial or clear cells and (B) deep or pigmented cells.

retina and is formed by polygonal cells filled with dark pigment. In my depigmented sections it showed cuboid cells, rather prismatic, with an agranular cytoplasm and a round nucleus (figs. 2-A and 8-B). The second layer is formed by bigger cells of variable size and prismatic in shape, many of them with a round and prominent free border, a rather ovoid nucleus and a slightly granular cytoplasm.

It can be seen that the superficial layer of the epithelium (processes, plicae, and interciliary areas) is formed by darker elements than those of the deeper layer which, with the Achúcarro-Río Hortega method shows cytoplasmic granules. Because of the peculiar shape of the ciliary body and its plicae, the sections offer a view of the elements along the length or width, sometimes the top or the root, and so the two layers of cells are projected in a frontal section and superimposed under the lens of the microscope. This previously made it difficult to decide whether the granular cells belong to both epithelial layers or only to the superficial one. Since the cytoplasmic argentophil granules do not exist in the pigmentary layer (fig. 2-A), this problem seems to have been solved.

The study by means of high-power achromatic objectives shows the aspect of the superficial layer, the main feature of which is the presence of granules in the cells. The characteristic of these cells are:

a. Not all the cells that cover the free surface of each ciliary process and ciliary region (figs. 2 and 3) have granules. The number of granular cells in each process varies but there are three main distributions: (1) granular cells; (2) agranular cells; (3) equal proportion of both. Sometimes all the cells of a row are granular but other times the granular cells alternate with agranular ones in various forms (figs. 2 and 7).

b. The granules have a polymorphous aspect: (1) the cytoplasm is spotted with little, perfectly rounded granules, slightly or

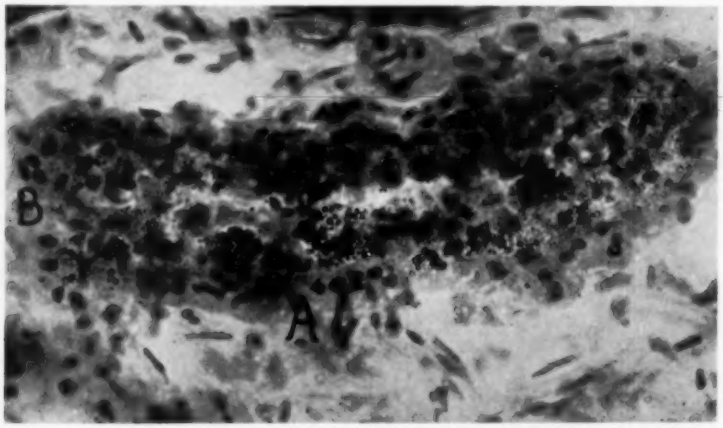


Fig. 2 (Sverdlick). Cross section of interciliary portion. (A) Deep epithelial layer, unpigmented and agranular. (B) Superficial epithelial layer with granular cells.

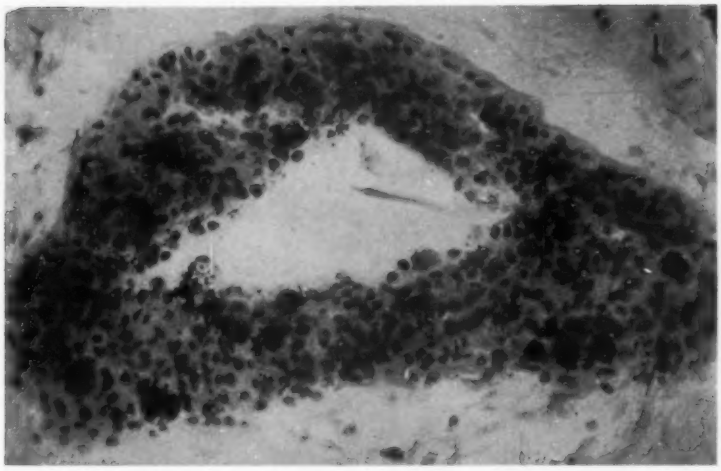

Fig. 3 (Sverdlick). Frontal projection of cross section of ciliary epithelial crypt, showing abundant granular cells.

intensely stained; (2) there is an equal proportion of large and small granules; (3) the granules are all large (figs. 4, 5, and 6).

c. Thus there exists in the cells of the superficial layer varying numbers of granules of various sizes, some are collected about the nucleus or are gathered in the center of the protoplasm. The different sizes of the granules possibly reflect their stage of growth.

d. The nuclei of these granular cells show no function related to the presence or absence of granules. It is difficult to demonstrate the characteristics of the chromatin

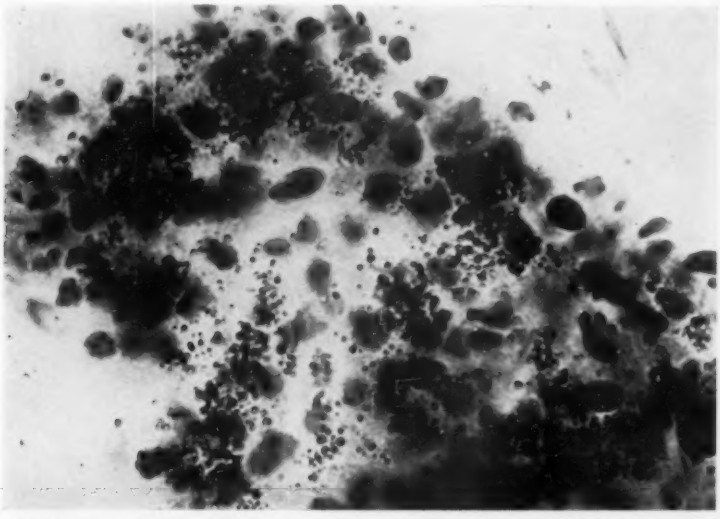

Fig. 4 (Sverdlick). Frontal projection of ciliary plicae, showing numerous epithelial elements with spherical granules of various sizes either disseminated or accumulated in clusters in the cytoplasm.

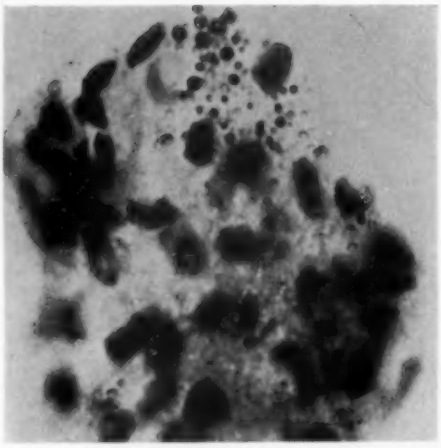

Fig. 5 (Sverdlick). Cytoplasmic granules located in the apex of a ciliary process.

of these nuclei because of the selectivity of the Achúcarro-Río Hortega method for staining granules. For this purpose the silver carbonate method was used and only the well-known characteristics of these nuclei were confirmed.

INTERPRETATION OF THE GRANULAR CELLS

a. The granules are seen in the superficial layer of the epithelium, figs. 2, 6, and 7. In each part of the ciliary body the number of granular cells is different. This might be explained in two ways: (1) the method used is not sufficiently selective; (2) in the epithelial cells there exists a peculiar mechanism by means of which the granules first appear and then disappear.

The first explanation is supported by the fact that the staining method is based on a mordant reaction followed by metallic impregnation and these reactions may not be complete. Thus might be explained the absence of granules in some complete ciliary processes and their irregular distribution of them in others. The second explanation is supported by the similarity to glandular cells in which the granular content and volume of the granules change according to the functional state of the cells. It may be possible that both explanations are correct, and the images obtained are due to functional variations according to the number and volume of the granules and also to incomplete staining because of limitations of the method.

b. It is evident that these granules are

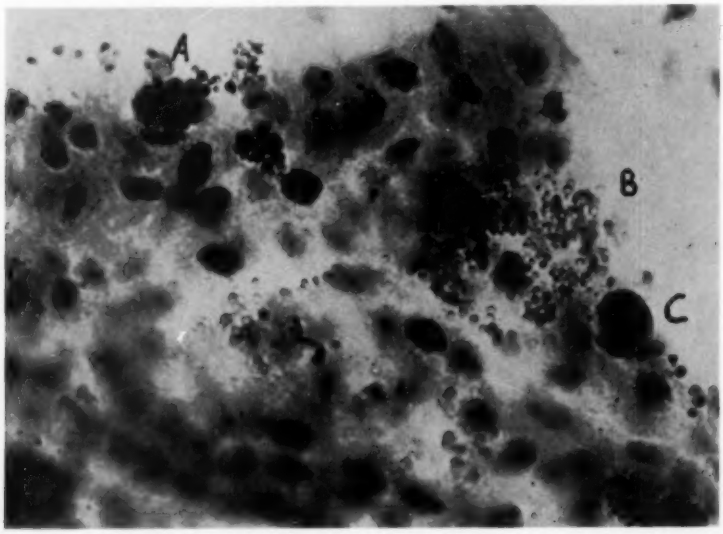


Fig. 6 (Sverdlick). Cytoplasmic granules in the ciliary epithelium. (A) Thick, mulberrylike clusters of granules. (B) Small dispersed granules. (C) Large intracellular sphere.

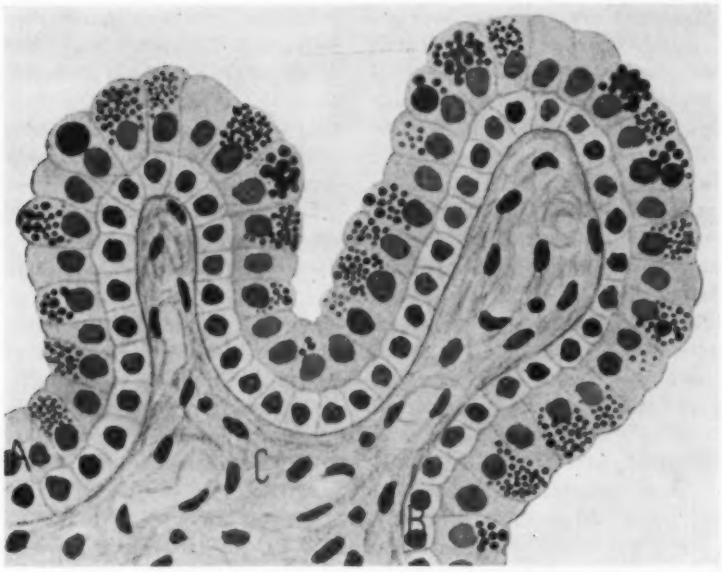


Fig. 7 (Sverdlick). Semischematic illustration of ciliary epithelial process with (A) superficial layer of granular cells and (B) deep layer of agranular cells (pigment decolored), (C) vascular connective network. The superficial cells show the location and variable aspect of the cytoplasmic granulations.

formed and afterward grow until they are transformed into larger bodies (fig. 7). This cycle of formation, growth, and disappearance by lysis is characteristic of zymogen granules of secretory cells, to which these granules undoubtedly are related. The only difference is that in these granules we could not observe the formation of half-moonlike inclusions corresponding to the fusion of the granules.

c. These observations point to the existence of a layer of epithelium at the free surface, composed of large cells, sometimes turgent, in which it is possible to prove a cystoplasmic elaboration of corpuscles similar to those of the secretary type. The zone in which these granules gather, that is, the upper pole of the cell, favors the hypothesis that, if this secretion really exists—as already believed by many authors, its products must flow into the chambers of the eye and not into the blood.

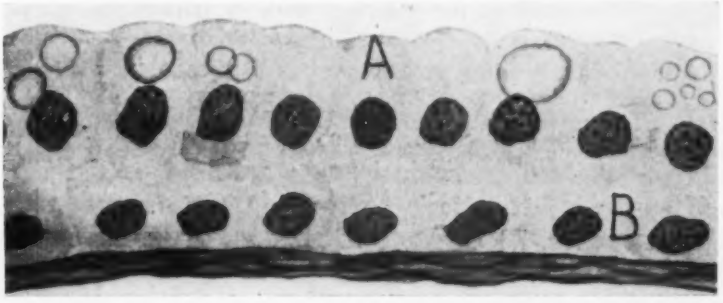


Fig. 8 (Sverdlick). The two layers of the ciliary epithelium, (A) superficial, with lipoid spherules and (B) deep, decolored.

Since Mawas, some workers have described accurately the mitochondrial organization of the cells being studied, and believed that the secretory activity of the ciliary body originated in them. But actually, even if the mitochondria were the substratum of the granules of secretion they cannot be the origin of the secretion because every cell, glandular or not, also has mitochondria. The granules here studied cannot be mistaken for mitochondria (which we could see in these cells) but they offer characteristics of a genuine cytoplasmic product.

Several authors described in the clear cells of the ciliary epithelium some spherules of lipoid nature, characteristic in their chromatic qualities. My study confirms the existence of these corpuscles but I believe them not to be related to those previously observed. The first group is seen when staining methods for fatty substances are used, and the second when a specific method for granules of secretion is used. The cells here studied have, therefore, mitochondria, as all cells, specific granules (perhaps of secretion), and spherules of lipoid nature whose significance is very different from the granules.

The similarity between the ciliary body and the choroid plexus is evident. If one secretes the aqueous humor, the other secretes the cerebrospinal fluid. Both have plicae with a vascular connective axis and an epithelial layer of cells. In both, plicae augment the functional surface. Nevertheless they differ in cellular origin; in one, the cells are a direct continuation of the retina and in the other the origin is the glial epithelium of the ependimum. Many authors and especially Zimman could not find evidence of specific granules in the choroid plexus, whose epithelium have mitochondria. Zimman, as others, saw and studied the lipoid spherules of many cells and ventured hypotheses. One of the ideas is that they represent regressive states in both cases. Another one, developed by Zimman, is that the spherules are merely the evidence of the storage of lipids by the cell.

Here we reach an important point in the activity of the ciliary body. We have evidence of cystoplasmic elaboration in the form of specific granules impossible to mistake with mitochondria or lipoid spherules. If the granules that we call specific evidence a secretory activity and the lipoid spherules are the result of the storage of lipids by the cell or the consequence of a breakdown of lipoproteic complexes, we would have two contradictory facts. If the first is an important basis for the secretory hypothesis, the second is a positive argument for the dialyzation theory. The conclusion would be, then, that the aqueous is a product of dialysis to which some products of cellular elaboration are added. But, which is its very nature?

Because of the aspects of the specific granules they seem to be formed of a lipoprotein substance or are granules of zymogen, if we keep in mind their selective staining qualities. Nevertheless, in the aqueous humor, lipids and proteins are scarce, salts in lower concentrations than in the blood and some organic substances in higher concentrations than in the blood being the main findings. The substance of the granules could be ascorbic acid, which has been found in the aqueous humor and is found in great proportion in the crystalline lens, an avascular organ in which ascorbic acid can be demonstrated by means of silver impregnations. It could be hyaluronic acid, found by Meyer and Palmer; that does not exist in the blood. In any case it would be necessary to study all of the substances remaining in the sections after the preliminary fixing and before staining. As of now, this matter remains unsettled.

There are some facts which should be stressed regarding the characteristics of the clear cells of the ciliary epithelium. These are (a) the vital staining because of the high content of oxidases (Schmelzer, Schall, Fisher); (b) the ability to fix the basic anilines (Friedenwald and Stiehler); (c) the modification in the content of chromatin of the nuclei; (4) the effect of pilocarpine

and eserine in enhancing or inhibiting secretions (Seidel). None of these details is definite evidence when considered alone, but if all facts are gathered, and the existence of specific granules in cells is added, the secretory theory of the ciliary body seems to be favored. The problem cannot be considered as definitely solved. More research is needed to clarify which factors influence the number of granules in the cells.

## Summary

By means of the first modification of the Achúcarro-Río Hortega staining method, it was possible to demonstrate in man and animals in the superficial layer of the ciliary body internal or clear cells. After depigmentation, could be seen granules which were characteristically different from mitochondria or lipoid vesicles; instead they showed the qualities of granules of secretion.

Because of the growth cycle and regularity of these "specific granules," and because the study was done with a selective method for different glandular granules, it can be said that these granules are products of cellular elaboration. Because of the zone in which they are placed, the upper layer of the cells being bathed by the aqueous humor, it is suggested that the granules are related to the mechanism of formation of aqueous, which contains also some substances not present in the blood. Although, for me, the secretory hypothesis has many positive findings in its favor, I must admit the possibility that the granules here described could be related to some of the organic components of the aqueous humor.

*Bmé. Mitre 1427.*

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# EXPULSIVE SUBCHOROIDAL HEMORRHAGE ASSOCIATED WITH CATARACT EXTRACTION*

## Report of a case with survival of the eye

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One afternoon several years ago while performing an operation for cataract on the only useful eye of a 42-year-old man I was confronted with "one of the most appalling experiences that may befall an ophthalmic surgeon."[1] As a successful intracapsular delivery of the lens of this patient's eye was completed, there was a gush of vitreous. When I looked into the eye to see what might be responsible for the precipitous loss of vitreous, I observed a dark reddish-brown mass in the vitreous chamber that increased in size as it welled toward the pupil. Although I had not previously encountered such a situation, the color of the expanding mass could mean only an expulsive hemorrhage from the choroid.

In those fleeting moments of my initial recognition of this feared complication, I recall a certain anguish that must affect all ophthalmic surgeons when a patient is hopelessly blinded by circumstances that we feel are beyond our control. But after those fractional seconds, I remembered reading somewhere (I knew not where) that such eyes had been saved by immediate sclerotomy and evacuation of the blood. The truth of the old proverb of legerdemainist that "the hand is quicker than the eye" permits me now to report the successful escape of both myself and the patient from a near catastrophe, with a follow-up period of seven years of the eye in question.

### Review of literature

Sir Henry Holland who has had one of the most extensive experiences with cataract surgery among our present-day ophthalmologists stated that expulsive hemorrhage is "the gravest of all complications at the time of surgery."[2] The gravity of this complication and its catastrophic effect on the future of the involved eye have been mentioned by all ophthalmologists who have written on the subject. Vail[3] aptly refers to the situation as the "bête noire of the ophthalmic surgeon."

As the reader can readily understand, attempts to evaluate the incidence of this dismal situation are probably altered by the reticence of ophthalmic surgeons to publish details of these unfortunate cases. However, most ophthalmologists consider this complication at the time of operation rare. Owens and Hughes[4] in a review of 2,086 extractions of uncomplicated senile cataract performed at the Wilmer Ophthalmological Institute found that expulsive hemorrhage at the time of operation occurred in one patient. Pfingst[1] observed two cases in a series of 2,500 extractions. In both of these cases the eyes became phthisic.

Pau[5] recently reported his observations on the incidence of expulsive hemorrhage in 1,520 cataract operations. He also collected 59 cases from the world literature in which expulsive hemorrhage occurred at, or at various intervals after, operations for cataract. In approximately a third (17 of these 59 cases) the hemorrhage had occurred at the time of extraction and in another third (22 cases) the hemorrhage occurred within 12 hours after operation.

Vail[3] first recorded the successful treatment of an expulsive hemorrhage following extraction of a cataract, with survival of the eye. Vail had the unusual experience of observing the expulsive hemorrhage at the

* From the Section of Ophthalmology, Mayo Clinic and Mayo Foundation. Read at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

time of the first dressing on the day following the operation. Vail's successful treatment of the hemorrhage was based on a prior report of Verhoeff.[6] To Verhoeff then goes the credit for devising a treatment for expulsive hemorrhage that has proved helpful to others faced with this catastrophe. In 1915, he told of a case in which the expulsive hemorrhage occurred at the completion of an operation for glaucoma. About four hours after operation Verhoeff performed several scleral punctures in the globe with release of the hemorrhage and survival of the eye.

Vail,[3] in addition to the case of hemorrhage following an operation for cataract, included in his report a case in which the expulsive hemorrhage followed iridectomy for glaucoma. A sclerotomy was performed immediately with release of the hemorrhage and survival of the eye.

The first instance of a hemorrhage occurring at the time of extraction of a cataract with the immediate and successful application of Verhoeff's sclerotomy was reported by Duehr and Hogenson.[7] In this case several factors, such as previous trauma to the eye, loss of fluid vitreous with collapse of globe during operation, and a difficult and prolonged delivery, may have contributed to the onset of the hemorrhage. In the case that I wish to report there do not seem to be any factors that, in retrospect, would have made it possible to have anticipated such a complication.

## Report of case

The patient, a man aged 42 years, came to the Mayo Clinic on January 17, 1951. He stated that he had had poor vision in each eye for approximately four years. On March 21, 1950, in a nearby city he had undergone an operation for cataract in the left eye. The patient felt that this eye had never healed satisfactorily, and the visual result was unsatisfactory.

Examination of the eyes revealed visual acuity of 20/200 in the right eye, and ability to recognize hand movements only with the left eye. An immature cataract, chiefly nuclear in type, accounted for the poor vision in the right eye. Bullous keratitis was present in the left eye. Absolute glaucoma eventually developed in this eye and necessitated evisceration in April, 1955. No further mention will be made of this eye. Refraction of the right eye in January, 1951, did not bring about any significant improvement in vision. The patient felt so handicapped in his occupation as a manager of a shoe store that he requested removal of the cataract, although he possessed the usual apprehensions so frequent among individuals who are confronted with an operation on their only useful eye.

The operation for removal of the cataract was performed on February 21, 1951. A survey of the patient's general physical status had not revealed any contraindication to this type of ocular operation. The patient was given the usual amounts of secobarbital (Seconal) and codeine (the drugs in standard use at that time) as preliminary medication. In the 11 minutes immediately preceding the operation a total of four cc. (12 mg.) of a preparation of d-tubocurarine was slowly administered by vein. The ocular rotations were then examined (as was customary) to determine whether the level of akinesia was adequate. Ten-percent solution of cocaine had previously been instilled on the surface of the eye for the purpose of analgesia.

A corneoscleral guide suture was placed at the limbus of the 12-o'clock meridian. A corneal section was made with the Graefe knife cutting the guide suture in the midportion of its tract. As the section was completed, there was a definite forward movement of the lens-iris diaphragm so that the anterior chamber became very shallow and the upper portion of the iris prolapsed between the lips of the incision. I made several attempts to reposit the iris into the anterior chamber, but I did not succeed. At this point I thought that the behavior of the eye might be due to squeezing of the globe by the extraocular muscles with a resulting elevation of the so-called "vitreous pressure." Another one cc. of d-tubocurarine was given intravenously to the patient. I waited a few minutes for the anterior chamber to deepen, and when it did not do so, I performed a complete sector iridectomy, although it had been my original intention to perform a "round pupil" extraction.

I grasped the lens near its lower pole with the capsule forceps and counterpressure was applied at the 6-o'clock limbus. I was agreeably surprised that the zonule gave way easily and the lens was rather quickly tumbled intact from the eye, for I had anticipated a tussle in performing an intracapsular extraction in an individual as young as this patient. My favorable inclinations toward the course of events in the preceding few minutes were quickly followed by consternation and near panic as the vitreous blurbed precipitously out of the eye and the unmistaken red-brown mass of expulsive hemorrhage from the choroid rose inexorably toward the pupil and its ultimate freedom from the confines of the eye.

At this point the initial double loop of a surgeon's knot was made in the corneoscleral suture and the gaping incision was approximated as well as possible against the rising intraocular pressure. The point of a Graefe knife was then plunged into the lower nasal quadrant of the globe along a line

corresponding to the ora serrata. A large amount of bright red blood immediately rushed through the sclerotomy and within a few seconds the brownish-red mass observed through the pupil seemed to collapse. Additional 5-0 black silk sutures were then placed across the incision at the 11- and 1-o'clock meridians of the limbus. By this time the seepage of blood through the sclerotomy had almost stopped but it became evident as I watched the color reflex through the pupil that the brownish-red mass was again forming. The Graefe knife was inserted again through the initial sclerotomy puncture and the blade slightly rotated. An additional mount of bright red blood gushed from the eye. When I was reasonably certain that no further decompression was possible by manipulation of the blade of the knife, the knife was withdrawn. The sclerotomy was not closed by sutures. When the tell-tale mass did not reappear in the pupil of the eye after a wait of several minutes, atropine was instilled and a patch was applied.

The eye was not disturbed for 40 hours. At the first dressing a small amount of reddish-tinged serum was observed on the bandage, the globe was congested, and the media were so hazy that the fundus of the eye could not be seen through the ophthalmoscope. A one-percent solution of atropine and a 2.5-percent solution of cortisone (Cortone) were dropped into the eye, and the eye was repatched. The eye was dressed daily thereafter. The congestion of the globe gradually subsided, and the media began to clear. As the interior of the eye became visible by ophthalmoscopy, a brownish-black reflex was noted across the two lower quadrants. This reflex was similar to that usually seen with choroidal detachments following operation for cataract. In several weeks the detachment of the choroid disappeared. One month after the operation, vision in the eye was 20/40 with a suitable correction for the aphakia. One and a half months after operation vision was 20/25 with the aid of a +7.25D. sph. ⊂ +1.5D. cyl. ax. 147°. On ophthalmoscopy a spotty pigmentation of the retina in the lower nasal quadrant was noted, similar to the pigmentation that follows surface diathermy.

By this time the progress and recovery of the eye had seemed so miraculous that the patient was dismissed. The future for the patient and his only useful eye seemed bright. Re-examination of the eye one year after operation, however, revealed an elevation of the intraocular pressure. Treatment with pilocarpine was started.

Subsequent examinations were performed at intervals of six months. Gradually the intraocular pressure increased and became resistant to control by miotics. The eye became sensitized to DFP (diisopropyl fluorophosphate) and eserine. Various drugs were used locally in the eye as a replacement for pilocarpine which had lost its effectiveness, but to no avail. By 1955, four years after the operation, the visual field began to show peripheral contraction. The topical measures were supplemented with oral administration of acetazolamide (Diamox), but the eye gradually became tolerant to this treatment and the intraocular pressure could not be lowered beyond the 35 to 40 mm. Hg range (Schiøtz).

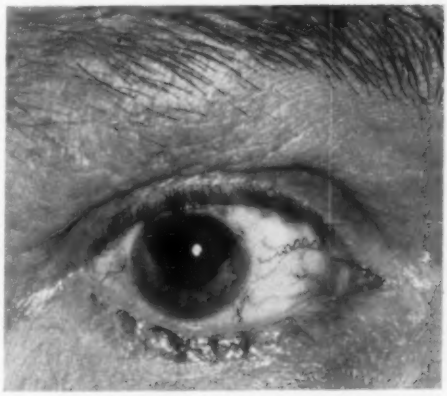

Fig. 1 (Henderson). Appearance of eye seven years after operation.

In August, 1956, cyclodiathermy was performed. This operation consisted of a single row of penetrating diathermy across the two upper quadrants of the pars plana of the ciliary body. The effect of this operation lasted for several weeks but then it was found necessary to resume the local instillation of a miotic.

In October, 1958, the patient was on a regimen consisting of the application of a four-percent solution of pilocarpine four times a day as drops into the eye and of ethoxzolamide (6-ethoxy-benzothiazole-2-sulfonamide) (Cardrase) 125 mg. twice a day. The intraocular pressure hovers in the high 20's and low 30's range of the Schiøtz tonometer. The color of the optic disc remains good but a rather large cup is present temporally. The isopters for the three-mm. white test object at one-third meter on the perimeter show a 10-degree nasal contraction and a 20-degree temporal contraction of the visual field. The corrected vision of the eye is not better than 20/40. The eye approximately seven years after operation is illustrated in Figure 1.

## Comment

The question of whether a calamitous complication such as expulsive hemorrhage at the time of intraocular operation can or cannot be prevented is debated in all of the publications and textbooks that have touched on this subject. Some observers consider that arteriosclerosis, vascular hypertension and senility may predispose to such a disaster and that proper selection of patients may lessen the chance of this complication. Since the patient just presented did not have any of

the attributes that are considered to predispose to expulsive hemorrhage and because I have operated on many older individuals with known weaknesses of the vascular tree without this complication, I am inclined to believe that expulsive hemorrhage occurring at the time of operation cannot be foreseen. Chandler,[8] in a recent symposium on the complications of cataract extraction, expressed a similar opinion.

Although an immediate evacuation of the blood by puncturing the globe with the point of a knife has seemed to be a factor in the successful outcome in the few cases reported in the American literature, other methods for handling the situation have been proposed. Gross and Fromaget[9] prevented loss of the eye by trephining the sclera. Regan,[10] who seemed to be dealing with a less violent type of hemorrhage in the case that he reported, performed venesection with withdrawal of 660 cc. of blood. Arruga[11] suggested an opticociliary neurotomy, which in his experience has permitted conservation of the eye in good condition. In recalling the alarming appearance of the eye in my case, I am dubious that an opticociliary neurotomy would have helped much. Several observers have proposed that the incision be quickly closed at the time of hemorrhage and the blood be evacuated from the eye several hours or several days later. With the present case in mind, I raise the question as to whether anything is to be gained by waiting. Finally, the method of management that seems most frequently employed should be mentioned, that is the eye is patched and the patch removed several days later.

The surgical manipulations required to release the expulsive hemorrhage among the eyes that have survived this complication varied a little in their applications. In the four cases previously published, a knife was used to open the globe. Verhoeff's case required three punctures in three different places, Duehr reopened the one sclerotomy in his case six times, and Vail was able to evacuate the blood in each of his cases by one puncture of the eye. In my case it was necessary to reopen the sclerotomy once.

In my case I estimated that less than 15 cc. of blood was lost and the hemorrhage seemed to stop within five minutes. In Duehr and Hogenson's case 30 cc. of blood were evacuated in 30 minutes.

The period of follow-up in one of Vail's cases was approximately two and one-half years and in the other case one month. In Duehr and Hogenson's case it was approximately six months.

## Summary

In the case presented an expulsive subchoroidal hemorrhage occurred at the time of a cataract operation on a 42-year-old man. The surgical manipulations employed to evacuate the blood and save the eye and the ultimate survival of the eye with useful vision have been described. Other interesting features of the case were the occurrence of this rare complication in the patient's only useful eye, the long period (seven years) of observation following operation, and the ultimate development of secondary glaucoma requiring further operation on the eye.

The case recorded represents the second published instance in the American literature of survival of an eye after an expulsive hemorrhage at the time of a cataract operation and the fifth in the American literature of survival following intraocular operation.

*Mayo Clinic.*

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# THE COURSE OF CHANGE IN SIZE OF SUCCESSFUL FILTERING CICATRICES*

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It has been commonly observed that an anemic-looking edematous filtering bleb is associated with successful filtering operations for glaucoma. Conversely, unsuccessful operations are characterized by flat cicatrices without the appearance of being swollen by fluid. It is the purpose of this paper to describe the observations made on the natural course of successful filtering blebs following trephining and iridencleisis operations. The blebs were photographed on color film at each visit of the patient, more frequently during the immediate postoperative period and every three to six months thereafter. During the period from January, 1957, to the end of March, 1959, the photographs were made stereoscopically, using a Donaldson camera. Fifty-eight eyes were thus studied photographically over a period of three to 112 months, averaging 24 months.

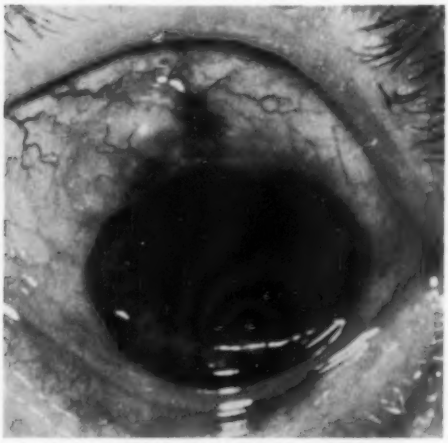

Fig. 1A (Sugar). Iridencleisis bleb after acute angle-closure glaucoma. Photographed December 9, 1957.

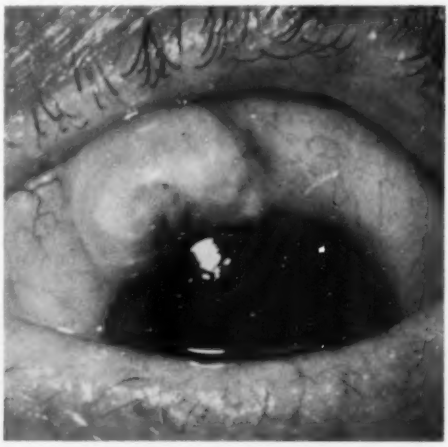

Fig. 1B (Sugar). Same as Figure 1A on April 29, 1958, showing increase in bleb size.

The series of 58 eyes consisted of 15 which were diagnosed angle-closure glau-

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Fig. 2A (Sugar). Iridencleisis bleb after acute angle-closure glaucoma. Photograph one week post-operatively (November 28, 1958).

Fig. 2B (Sugar). Same eye as Figure 2A four months later (March 30, 1959), showing increase in bleb size.

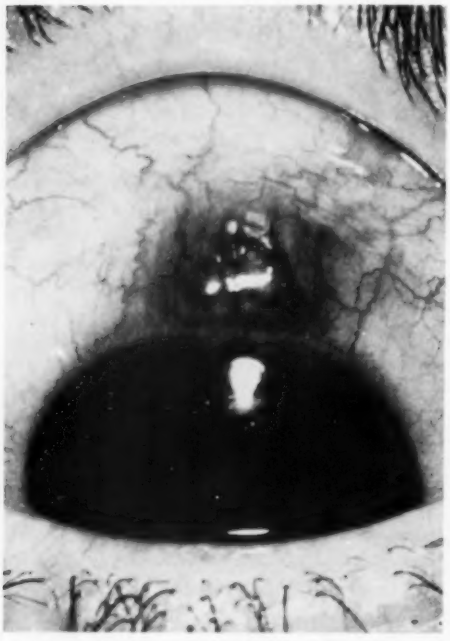

Fig. 3A (Sugar). Iridencleisis bleb after acute angle-closure glaucoma. Photograph December 9, 1957.

coma, five secondary glaucoma and 38 chronic simple glaucoma.

Of the 15 eyes with angle-closure glaucoma, all had iridencleisis operations. In seven the bleb increased in size over the five to 112-month period of observation (figs. 1A

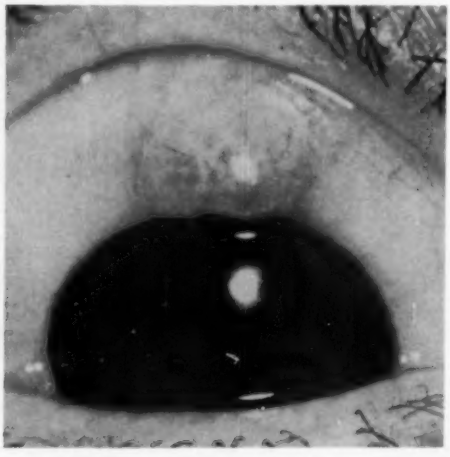

Fig. 3B (Sugar). Same eye as Figure 3A four months later (April 8, 1958), showing increase in bleb size.

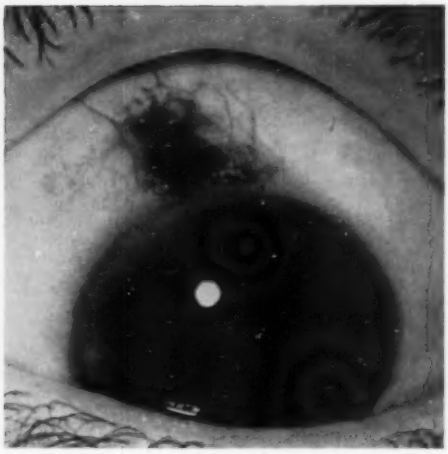

Fig. 4A (Sugar). Iridencleisis bleb after acute angle-closure glaucoma. Photograph December 4, 1957. Appears flat.

Fig. 4B (Sugar). Same eye as Figure 4A, 13 months later (January 22, 1959), showing marked change in bleb size.

to 4B). In one the bleb decreased (15-month observation period) and in seven it remained unchanged (during a six- to 100-month observation period).

Of the five eyes with secondary glaucoma, all had trephining operations. Two were postuveitic glaucomas and three pigmentary glaucomas. The two eyes with postuveitic glaucoma had an increase in bleb size during the period of observation of 12 to 27 months. Of the eyes with pigmentary glau-

Fig. 5A (Sugar). Trephination bleb after simple glaucoma. Photograph May 25, 1956.

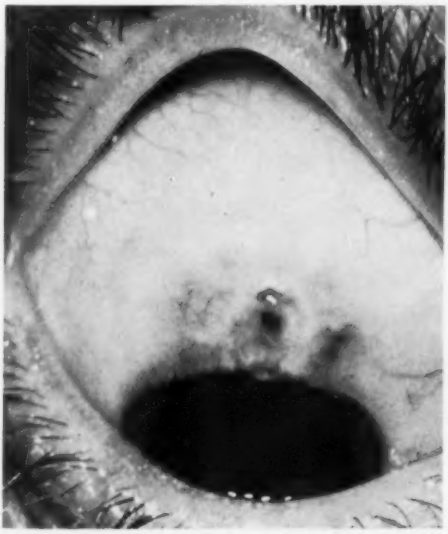

Fig. 5B (Sugar). Same eye as Figure 5A, 33 months later (March 13, 1959), showing increase in bleb size.

Fig. 6A (Sugar). Iridencleisis bleb after simple glaucoma. Photograph five days postoperatively, January 20, 1958.

Fig. 6B (Sugar). Same eye as Figure 6A, 11 months later (February 13, 1959), showing increase in bleb size.

coma, one bleb increased in size and two decreased (during a 23- to 26-month observation period).

The 38 eyes with simple glaucoma included three in which trephination had been followed by late infection which cleared completely, leaving smaller blebs. Of the remaining 35 uncomplicated eyes, 14 blebs increased in size over a period of five to 43 months of observation (figs. 5A to 7B),

Fig. 7A (Sugar). Trephination bleb after simple glaucoma. Photograph November 30, 1957.

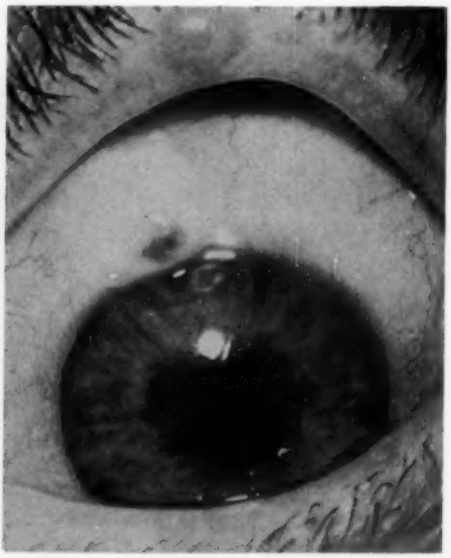

Fig. 7B (Sugar). Same eye as Figure 7A, 13 months later (January 9, 1959), showing increase in bleb size.

Fig. 8A (Sugar). Trephination bleb after simple glaucoma. Photograph April 3, 1954.

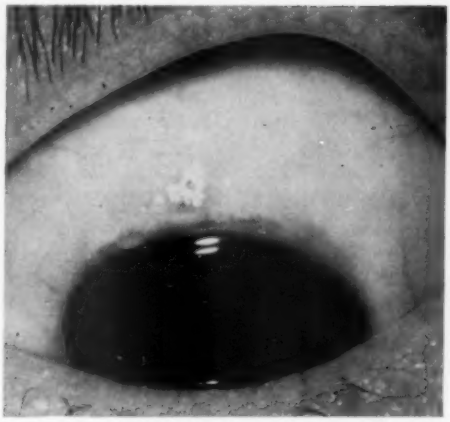

Fig. 8B (Sugar). Same eye as Figure 8A, 55 months later (November 28, 1958), showing decrease in bleb size. Tension remained normal.

nine decreased in size during a three to 51-month period (figs. 8A to 9B) and 11 remained unchanged (during a three to 43-month period). One increased in size during its early four-month course and then decreased during the next five months.

Thus a total of 58 successfully operated glaucomatous eyes showed an increase in the size of the filtering bleb in 24 (41.3 percent), a decrease in 15 (25.8 percent), no change in 18 (31.0 percent) and an increase followed by a decrease in one (1.7 percent). Table 1 shows the breakdown of these figures.

## Comment

From the viewpoint of clinical observation it was not possible to evaluate the change in appearance of the blebs. Descriptions of the bleb indicated only whether it was functioning and whether it was large or small, cystic or noncystic. The photographic

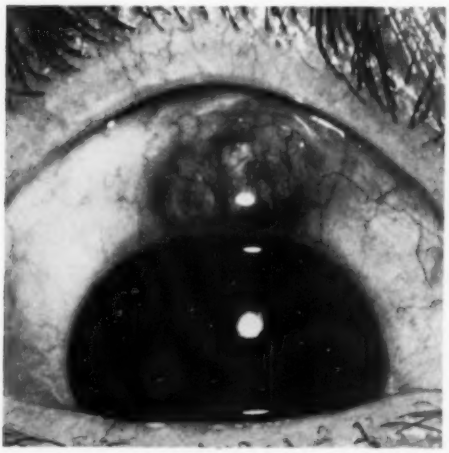

Fig. 9A (Sugar). Iridencleisis bleb after simple glaucoma. Photograph January 13, 1958.

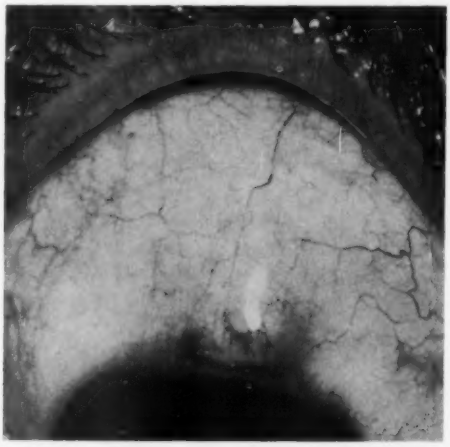

Fig. 9B (Sugar). Same eye as Figure 9A, one month later (February 18, 1958), showing decrease in size of bleb. Tension remained normal.

TABLE 1

CHANGES IN FILTERING BLEBS FOLLOWING IRIDENCLEISES AND TREPHINATIONS

| Type of Glaucoma | Type of Operation | Number of Eyes in Which Bleb | | | | Total Number of Eyes |
|---|---|---|---|---|---|---|
| | | Increased in Size | Decreased in Size | Remained Unchanged | Increased, then Decreased | |
| Angle-closure | All iridencleises | 7 | 1 | 7 | 0 | 15 |
| Secondary | | | | | | |
| postuveitic | All trephinations | 2 | 0 | 0 | 0 | 2 |
| pigmentary | | 1 | 2 | 0 | 0 | 3 |
| Simple | | | | | | |
| after late infection | All trephinations | 0 | 3 | 0 | 0 | 3 |
| uncomplicated | 27 trephinations<br>8 iridencleises | 14 | 9 | 11 | 1 | 35 |
| TOTALS | | 24 | 15 | 18 | 1 | 58 |

changes were quite dramatic when comparisons of the photographs were made. Sixty-nine percent showed changes while 31 percent did not. Thus, roughly two thirds of successful blebs changed, and roughly two thirds of these showed an increase in bleb size during the period of observation. The period of increase appeared to extend over the entire period rather than just the early postoperative period.

In attempting to explain the changes in the appearance of the bleb, Teng, Chi and Katzin* and Maumenee† have suggested that there is a breakdown of collagen in Tenon's capsule by the aqueous in instances where blebs are functioning successfully. This appears to be indicated by the gradual formation of cystic areas in blebs which have previously been noncystic.

## SUMMARY AND CONCLUSIONS

A series of 58 glaucomatous eyes, successfully operated with filtering procedures, showed a previously unsuspected change in the size of the filtering blebs in 69 percent of eyes. Sixty-two percent of these increased in size. These filtering cicatrices are, therefore, not static but change with time. This is compatible with our experience that blebs which filter poorly at first may later function well, while some which are successful early may later become nonfunctioning.

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* Teng, C. C., Chi, H. H., and Katzin, H. M.: Histology and mechanism of filtering operations. Am. J. Ophth., **47**:16, 1959.

† Maumenee, A. E.: Meeting of Wilmer Residents A., March, 1959.

# EPIDEMIC KOCH-WEEKS CONJUNCTIVITIS AND TRACHOMA*

## In the Coachella Valley of California

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Seasonal outbreaks of purulent conjunctivitis have have recorded in the Near East since ancient times.[1] Studies done in Egypt have suggested that the seasonal bacterial conjunctivitis is an important factor in the spread of trachoma.[2] This report deals with the etiology and epidemiology of seasonal conjunctivitis in the southwestern United States and records the close association of this bacterial infection with trachoma and phlyctenular keratoconjunctivitis.

Acute conjunctivitis occurring in seasonal epidemics from May to October has been recorded in the Coachella Valley of southern California for 30 years.[3] Conjunctival smear findings have incriminated the Koch-Weeks bacillus (Hemophilus aegyptius) as the etiologic agent.[4] Similar epidemics of seasonal conjunctivitis have occurred in the lower Rio Grande valley of Texas and in Georgia.[5,6] In all these areas the epidemics have been closely associated with a small fly commonly known as the "eye gnat," Hippelates pusio in Georgia and Texas, Hippelates collusor in California.[7]

The conjunctivitis is extremely purulent and associated with marked edema of the lids. Young children are most frequently affected, and there is apparently little immunity, one individual often having repeated attacks during a season.[5,6] The incubation period in experimental cases is six hours,[8] and the untreated case lasts from 10 to 12 days.[2]

The bacillus, a slender gram-negative rod, was first observed in cases of epidemic conjunctivitis in Egypt by Koch in 1883.[9] Weeks isolated the organism in 1886, succeeded in carrying it in serial culture, and finally produced a characteristic conjunctivitis in volunteers with the subcultured strains.[10] The biologic characteristics of the bacillus have been elucidated by Davis and Pittman who studied 61 strains isolated from cases of conjunctivitis in Texas.[11,12] Although H. aegyptius and nontypable strains of H. influenzae are similar in most respects, H. aegyptius has a group-specific antigen, reduces nitrates to nitrites, is unable to ferment xylose, does not produce indole, has a more elongated form, and most significantly, produces a hemagglutinin for human red blood cells. In two recent studies[13,14] however, hemagglutination was found to have no relationship to the pathogenicity of a series of Hemophilus spp. isolated from the conjunctiva.

A careful study done in Texas by Davis and Pittman[6] revealed that the disease was prevalent from May to October, reaching a peak in the early fall, and that one to four-year-old children had the highest rate of infection. Hemophilus spp. were isolated from one half the cases, and there were only a few other ocular pathogens. An epidemiologic survey of seasonal pink eye in Georgia showed a May to October season and a peak incidence in preschool children.[5] A study of school children in the same area demonstrated that grades 1 to 3 had the highest rates, that there were more cases in the rural schools, and that the seasonal peak was reached in the fall months.[15] In Egypt, Koch-Weeks conjunctivitis has a similar age distribution but two seasonal peaks, one in May and

* From the Epidemic Intelligence Service, Communicable Disease Center, U.S. Public Health Service, and the Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco. I wish to express my gratitude to Dr. Mir S. Mulla, Department of Entomology, University of California, Riverside; to Mr. Arthur Cavanaugh and other members of the Coachella Mosquito Abatement District; to Dr. Everett Stone, the Riverside County Health Officer; and to Dr. and Mrs. Phillips Thygeson for their advice and assistance during the course of this investigation and with the preparation of the manuscript.

another in September.[2] About one half the children under the age of six years in one Egyptian village were shown to be symptomless carriers of the Koch-Weeks bacillus during the winter months; with the coming of warmer weather these carriers developed symptoms and served as multiple foci for the seasonal epidemic.[16]

It has not been possible to establish that the eye gnat (H. pusio or H. collusor) plays any role in the spread of Koch-Weeks conjunctivitis in the United States; its close association with the disease, however, is incontestable: (a) the insect is peculiarly attracted to the conjunctiva, and for this reason constitutes a major nuisance in infested areas; (b) the gnat and pink eye seasons coincide; and (c) only those areas of the United States that are heavily infested with eye gnats are troubled with seasonal Koch-Weeks conjunctivitis. In Egypt a similar relationship has been postulated between seasonal conjunctivitis and a species of house fly (Musca sorbens). Wilson[2] demonstrated a parallel rise in Koch-Weeks infections and the fly population during the spring months, and a decline in both when the high summer temperatures reduced fly breeding. With the coming of cooler temperatures in the fall of the year, the fly population again increased along with the incidence of H. aegyptius infections. Vigorous fly control in one Egyptian village actually reduced the number of clinical cases although the carrier rate remained the same.[17]

The present study was undertaken in an effort to confirm the suspected etiology of the seasonal conjunctivitis occurring in the Coachella Valley of California, and to study the epidemiology of the disease with particular reference to the role of the eye gnat.

## Seasonal conjunctivitis in the Coachella Valley, 1951-1957

### Geography and economy[18]

The Coachella Valley is a roughly triangular area in southeastern California lying between the San Jacinto mountains on the west, the Chuckwalla and Chocolate mountains on the northeast, and the Salton Sea on the south. The valley floor is almost entirely below sea level. The area is part of the Colorado Desert, and has a climate typical of the desert with mild winters, intensely hot summers and a low annual rainfall. The economy of the valley is dependent primarily on agriculture and tourists; about 80,000 acres are under cultivation, and the Palm Springs area draws many winter visitors. Because of the large-scale farming operations, many people of Mexican ancestry have settled permanently in and near the towns in the southern part of the valley. There are also numbers of migrant workers who live in labor camps during the harvesting season.

### Epidemiology

Since 1951, the local grammar schools have sent monthly summaries of the number of cases of pink eye to the Coachella Valley Mosquito Abatement District, which is devoted primarily to eye-gnat control. These summaries and the records of the seasonal variation of the gnat population in the valley were made available by the Abatement District, and meteorologic data were obtained from U. S. Weather Bureau reports.[19]

The seasonal incidence of conjunctivitis in one grammar school from 1952 to 1957 is shown in Figure 1, along with the concomitant mean monthly temperatures, and the number of Hippelates collusor caught in eight traps from March, 1956, to November, 1957.

It can be seen that the incidences of both pink eye and eye gnats were related to seasonal fluctuations in temperature. These data are remarkably similar to those obtained by Wilson[2] in Egypt on the seasonal variations of temperature, ophthalmia, and flies.

Table 1 gives the yearly incidence of pink eye in two elementary schools, one in the town of Coachella, the other in Indio, three miles away. The Coachella school has a high percentage of students from a low economic stratum of society, whereas the Indio school has a large number of children from middle

TABLE 1

INCIDENCE OF PINK EYE IN GRAMMAR SCHOOL CHILDREN (COACHELLA AND INDIO, CALIFORNIA) AND THE NUMBER OF GNATS TRAPPED

| School Year Beginning: | Incidence of Pink Eye Cases per 100 Pupils per Year | | Gnats per Trap (in thousands) |
|---|---|---|---|
| | Coachella | Indio | |
| 1951 | 95.6 | 22.9 | — |
| 1952 | 37.2 | 9.5 | 45.6 |
| 1953 | 33.4 | 5.8 | 65.0 |
| 1954 | 23.2 | 5.3 | 49.8 |
| 1955 | 19.9 | 1.5 | 18.1 |
| 1956 | 17.7 | — | 32.5 |
| 1977 | 26.2 | 9.2 | 67.8 |

class homes. The number of gnats per trap caught during the same period is presented in the same table.

While the general trend of the incidence of pink eye in the two schools was the same, Coachella had a much higher infection rate. This may have been a reflection of the different socio-economic backgrounds of the children attending the two schools, or may have been due to a disparity in the nurses' interest in the problem at the two schools. The quantitative shift in gnat population appears to have had little connection with fluctuations of the disease during this period. There was a steady decline in the incidence of conjunctivitis from 1951 to 1956, with a slight increase in 1957. The local physicians and school nurses independently expressed the opinion that seasonal pink eye was much less severe than it had been in the past.

The incidence of pink eye by grade in one school is presented in Table 2. These figures resemble similar data from Georgia[15] and emphasize the fact that the disease is more common among young children.

## FIELD STUDY, OCTOBER, 1958

### EPIDEMIOLOGY

In order to estimate the incidence of seasonal conjunctivitis in the general population

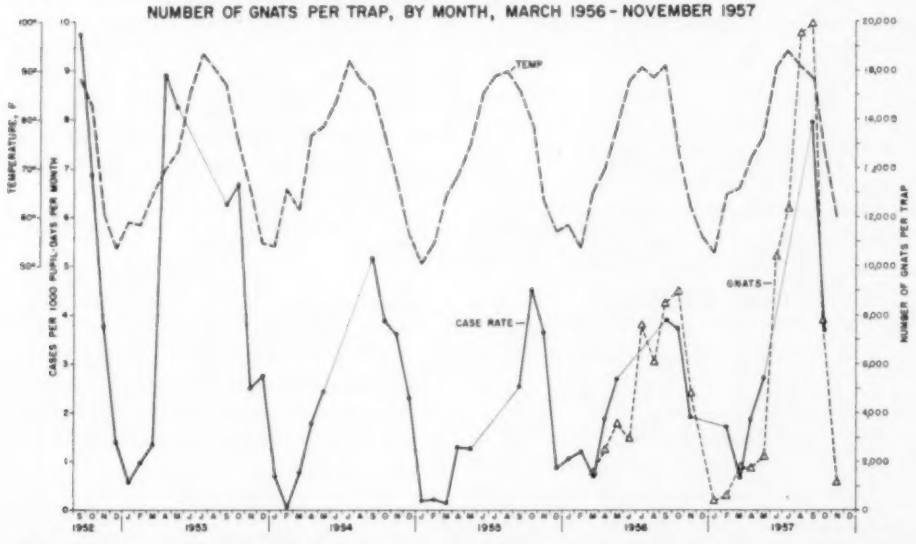


Fig. 1 (Dawson). Variation of the incidence of conjunctivitis and eye gnats with mean monthly temperatures. The lighter portions in the case rate line represent the three summer months when no data were available from the school during its annual vacation.

TABLE 2

INCIDENCE OF PINK EYE IN THE PALM VIEW SCHOOL, COACHELLA, CALIFORNIA, FROM SEPTEMBER TO NOVEMBER, 1956, AND FEBRUARY TO MAY, 1957

| Grade | Cases per 100 Pupils Enrolled |
|---|---|
| Kindergarten | 74.3 |
| 1 | 36.0 |
| 2 | 23.1 |
| 3 | 12.3 |
| 4 | 4.6 |
| 5 | 13.2 |
| 6 | 8.9 |
| 7 | 0.9 |
| 8 | 0 |

of the Coachella Valley, a house-to-house survey of a Spanish-American section (Coachellita) of the town of Coachella was conducted in October, 1958. The results are presented in Table 3. The area surveyed is geographically isolated from the rest of the community and was chosen because it contained the homes of a large number of the children found with the disease in the local school. All homes in this section were visited and the occupants interrogated as to the number of cases of pink eye in the household since May. Usually the mother or grandmother answered for the whole family.

Although the figures presented in Table 3 no doubt reflect underreporting, they probably give a rough approximation of the age distribution of seasonal conjunctivitis in a heavily attacked population. Information on a total of 499 individuals (240 males and 259 females) was recorded; there were 169 cases of pink eye with a steady decline in incidence from the age of one year to the age of 19 years. The peak incidence occurred in the one- to four-year-olds, but the rates continued to remain high through the 10- to 14-year age group, particularly among females.

TABLE 3

AGE SPECIFIC INCIDENCE OF PINK EYE AMONG 499 PERSONS IN COACHELLITA, MAY TO OCTOBER, 1958

| Age (yr.) | Males Cases/ 100 Persons | Females Cases/ 100 Persons | Both Sexes Cases/ 100 Persons | Number of Persons Included in Survey |
|---|---|---|---|---|
| 0– 1 | 44 | 40 | 43 | 21 |
| 1– 4 | 51.5 | 65.2 | 58.0 | 78 |
| 5– 9 | 48.2 | 47.1 | 47.5 | 122 |
| 10–14 | 29.7 | 46.9 | 38.7 | 69 |
| 15–19 | 10 | 27 | 19 | 42 |
| 20–29 | 8.7 | 0 | 3.8 | 53 |
| 30–39 | 0 | 17 | 8.6 | 58 |
| 40–49 | 0 | 27 | 15 | 20 |
| 50–59 | 0 | 0 | 0 | 12 |
| 60+ | 0 | 0 | 0 | 9 |
| Not stated | 22 | 33 | 27 | 15 |
| TOTAL | 27.5 | 36.7 | 32.2 | 499 |

It could not be shown in this single survey that a high rate of secondary infections obtained within households, as was noted by Davis and Pittman.[6] There were eight cases among the 30-to-39 and the 40-to-49-year old women, an attack rate of 20 percent. All of these women had families with young children, and in five cases one or more of the children in the family had a concomitant conjunctivitis. These women may have had a high incidence of infection as a result of spending most of their time around the home exposed to young children, who are the most heavily infected portion of the population. Similarly, the slightly higher rates in adolescent girls than in adolescent boys may well have been due to the fact that the young girls are kept close at home (and thus to their younger siblings) in a community whose cultural background is predominantly Spanish.

The number of cases occurring each month were:

| | |
|---|---|
| May | 6 |
| June | 17 |
| July | 15 |
| August | 34 |
| September | 45 |
| October 1-10 | 44 |

In view of the retrospective nature of the survey, it is quite probable that the more recent cases were recalled more easily, thus giving a larger number of cases reported in recent months.

## CLINICAL OBSERVATIONS

All children referred with pink eye to the school nurse at the Palm View School in

Coachella during the two-week period of this survey were examined clinically with a binocular loupe and hand illuminator. At the same time culture materials were taken from their conjunctivas and lids. In addition several children and one adult with acute conjunctivitis discovered during the house to house survey of Coachellita were also examined and cultured.

The total of 41 individuals so examined were diagnosed as follows:

| | Cases |
|---|---|
| Acute purulent conjunctivitis | 32 (78%) |
| Active trachoma | 28 (68%) |
| Phlyctenular keratoconjunctivitis | 5 (12%) |
| Acute follicular conjunctivitis with preauricular node and mononuclear conjunctival exudate; presumptive diagnosis: Adenovirus infection | 1 (2.4%) |

The majority of the cases of trachoma were diagnosed on the basis of follicles on the upper tarsal plate and either Herbert's pits or a grossly visible pannus. In a small group in which the gross findings were indecisive, the children were examined with a slitlamp by Dr. Kenneth Grow* and me to verify the presence of pannus or the keratitis characteristic of the disease. The cases of phlyctenular keratoconjunctivitis were identified on the basis of one or more characteristic active phlyctenules at the limbus, associated with conjunctival hyperemia or by the residual corneal scars of the disease.

These assorted infections occurred in the following diagnostic combinations:

| | Cases |
|---|---|
| Bacterial conjunctivitis alone | 11 |
| Trachoma alone | 4 |
| Trachoma and bacterial conjunctivitis | 20 |
| Trachoma and phlyctenular keratoconjunctivitis | 4 |
| Trachoma, bacterial conjunctivitis, and phlyctenular scars | 1 |
| Trachoma and acute follicular conjunctivitis | 1 |

* Dr. Grow, an ophthalmologist in Palm Springs, kindly volunteered his assistance in making the clinical diagnosis of trachoma in this group of children.

### Bacteriology

Blood-agar plates and Fildes' peptic digest of sheeps' blood in beef heart infusion agar were used for primary isolation in all cases, the latter particularly for the isolation of Hemophilus spp.[6] All cultures were incubated 24 hours, then mailed to the bacteriology laboratory of the Francis I. Proctor Foundation for Research in Ophthalmology at the University of California Medical Center in San Francisco. These were again incubated overnight and read. Hemagglutination tests were performed as suggested by Davis, et al.[12] by mixing 0.5 ml. of a heavy suspension of the isolated, subcultured strain of Hemophilus with 0.5 ml. of a 0.5-percent suspension of washed human red cells. The test was considered to be positive when either grossly visible clumping occurred or a uniform blanket of red cells covered the bottom of the tube.

Of the 41 cultures taken, nine yielded small colonies characteristic of the Hemophilus group. Seven of these were successfully maintained in serial culture on Levinthal's medium. All nine isolations were from cases of acute purulent conjunctivitis; there was no instance of isolation from eyes that were not acutely inflamed. Six of the seven subcultured strains produced agglutination of human red blood cells, supposedly a characteristic property of H. aegyptius. Two control strains of Hemophilus from cases of meningitis, and one strain isolated from the conjunctiva, failed to produce hemagglutination. Koch-Weeks bacillus was the only bacterial pathogen isolated, and is undoubtedly the etiologic agent of the seasonal conjunctivitis in this area.

### Eye gnats

Eleven pools of eye gnats were trapped; five of them were caught in the vicinity of houses, and six were taken with a hand aspirator from the faces of children with acute purulent conjunctivitis; cultures from conjunctivas of these children grew out Hemo-

philus in four instances. The flies were washed in sterile saline for external flora, then ground in the same saline for internal flora; in each instance a loopful of the saline was streaked out on the blood agar and Fildes' medium.

In no case were any Hemophilus or other eye pathogens found in the flora of the eye gnats; coliform organisms, Staph. albus, and Monilia were the most common micro-organisms recovered. In most cases the growth of coliform organisms on the plate was so massive that more delicate organisms would have been crowded out. These results can therefore not be regarded as conclusive evidence that Hippelates flies are not vectors of Hemophilus spp.

## Discussion

Finding clinical trachoma in this area was totally unexpected. Trachoma was known to be prevalent in the Coachella Valley from 1925 to 1940,[20] 20 to 250 cases a year being reported from this county. While trachoma is a comparatively rare disease in the white population of the United States, its association with seasonal Koch-Weeks conjunctivitis in the Near East has been well documented. In Egypt, Wilson[2] recorded the fact that children born during the conjunctivitis season contracted trachoma by the age of three or four months, while those born during the winter months were not infected with trachoma until eight to 10 months. The same author periodically examined the eyes of 50 Egyptian infants and found that in 34 trachoma was preceded by an acute ophthalmia. Similarly Pagès[21] in Morocco has published data supporting the idea that any conjunctivitis makes the eye more suspectible to invasion by another organism, Koch-Weeks infections "opening the door" for the less contagious virus of trachoma.

While no causal relationship could be demonstrated between Koch-Weeks conjunctivitis and trachoma in the present study, diseases were often prevalent in the same household, the following family being an extreme example:

Case no. 30-P-B. June Moreno, a four-year-old girl, had had an acute bilateral conjunctivitis for five days. Both lids were swollen, there was a purulent discharge, and large preauricular nodes were present. In addition, there were follicles on the upper tarsal plate indicative of trachoma. Hemophiluslike colonies grew out on blood agar and Fildes' medium but could not be subcultured. Her siblings presented a variety of pathologic states: Brothers, aged 11 and five years, had trachoma and acute conjunctivitis, and H. aegyptius was isolated from each; a sister, aged seven years, had trachoma and a conjunctivitis which was negative on culture; another sister, aged nine years, was symptomless, but had trachoma IIA; a third sister, aged 13 years, had a normal conjunctiva; two infants, aged seven months, were not seen, but were reported to have pink eye. The mother, aged 42 years, was not examined, but said she had had two episodes of pink eye in the previous month.

Phlyctenular keratoconjunctivitis is a common sequela of Koch-Weeks infections. The presence of phlyctenules was recorded by Weeks[10] in one of his experimental inoculations and has been noted by other authors following seasonal conjunctivitis.[6] Repeated episodes of phlyctenulosis are capable of producing severe corneal scarring and are a major cause of blindness in some areas.[22] It is generally accepted to be a hypersensitivity reaction to bacterial proteins, most commonly to products of the tubercle bacillus[23] but occasionally also to the products of other microbial agents, such as the Staphylococcus and C. immitis.[24] It is also known that nonspecific conjunctival inflammations produced by various agents may precipitate an attack of phlyctenulosis in a tuberculous child. It has been postulated that episodes of Koch-Weeks conjunctivitis trigger attacks of phlyctenulosis in such children.

The relationship between the annual increase in the number of cases of conjunctivitis and of eye gnats, with rising temperatures in the spring, still remains obscure. Even in Egypt, where there is strong evidence that the house fly is a vector,[2,17] Hemophilus spp. were found in only six of sev-

eral hundreds of pools of flies.[25] It may be, however, that the eye gnat plays an indirect role, traumatizing the conjunctiva and thus increasing its susceptibility. Russian investigators[26] have shown that it is possible to produce H. aegyptius infections in rabbits (ordinarily an immune species) by cauterizing the conjunctiva before inoculating it with the bacteria.

No evidence of symptom-free carriers of H. aegyptius was found in the Coachella Valley. The strains isolated were obtained only from hyperacute cases, no isolations being made from even mild or convalescent episodes of conjunctivitis, nor from patients with other disorders. Similarly, weekly cultures of the conjunctivas of 75 Egyptian children for two months failed to reveal any carriers of Hemophilus spp.[25] Huet,[14] on the other hand, recovered Hemophilus from the conjunctivas of 25 percent of healthy Tunisian children and 29 percent of those with acute conjunctivitis. This author postulates two species of Hemophilus in the conjunctiva, one a saprophyte, the other pathogenic, which are indistinguishable by the usual bacteriologic methods.

## Summary and Conclusions

1. Epidemic conjunctivitis in the Coachella Valley of southeastern California occurs from May to October and is predominantly a disease of children. The Koch-Weeks bacillus (Hemophilus aegyptius) is the etiologic agent in this area.

2. In a series of 41 patients with conjunctivitis examined in the course of a two-week survey, 28 (68 percent) were found to have trachoma, and four (12 percent) to have active phlyctenulosis. It is suggested that seasonal Koch-Weeks conjunctivitis is a factor in the spread of trachoma in this area as it is in the Near East.

3. Although eye gnats (Hippelates collusor) are closely associated with H. aegyptius conjunctivitis in the Coachella Valley, it was not possible to demonstrate their precise role in the spread of the disease.

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# USE OF ECHOTHIOPHATE (PHOSPHOLINE IODIDE†) IN THE TREATMENT OF GLAUCOMA*

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Drugs causing cholinesterase inhibition have long been known to be effective in lowering intraocular pressure when applied to glaucomatous eyes. Those drugs which inhibit cholinesterase include di-isopropyl fluorophosphate (DFP), tetraethylpyrophosphate (TEPP), physostigmine, neostigmine, diethyl-p-nitrophenylphosphate (Mintacol) and demecarium bromide (BC-48).[5,6] Many attempts have been made to produce a drug with the long action of DFP but with greater stability in aqueous solution and without undesirable side effects such as ciliary congestion, severe miosis, pseudocysts of the iris, and occasional detachment of the retina. One product of such attempts is echothiophate, first synthesized in 1956, and found to have considerable potency as a long-acting cholinesterase inhibitor.[1]

Leopold, Gold, and Gold used echothiophate in the treatment of glaucoma.[2] They found the drug effective in lowering intraocular pressure, especially in the treatment of open-angle glaucoma and in so-called aphakic glaucoma.

The present study was undertaken to evaluate independently the effectiveness of echothiophate as an ocular hypotensive agent in glaucomatous eyes.

## I. METHOD

### 1. PREPARATION OF DRUG

Echothiophate comes from the manufacturer as a white crystalline powder, readily soluble in water. The drug was dissolved in isotonic saline, and 0.5-percent chlorobu-

* From the Glaucoma Consultation Service, Massachusetts Eye and Ear Infirmary. A portion of this paper was presented at the Massachusetts Eye and Ear Infirmary Alumni Meeting, April 16, 1958, Boston. This investigation was supported by Research Grant B-218 from the Institute of Neurological Diseases and Blindness of the National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland.

† Echothiophate is the A.M.A. generic name for 2-diethoxyphosphinyl-thioethyltrimethyl ammonium iodide (217-Methyl Iodide). The Campbell Pharmaceutical Company, New York, New York, provided the echothiophate (trade name, Phospholine Iodide) used in this study.

tanol was added as a preservative. The drug was sterilized by ultrafiltration and dispensed in ¼ oz. dropper bottles in concentrations of 0.125-percent and 0.25-percent (Massachusetts General Hospital Pharmacy).

### 2. Criteria for intraocular pressure control

All measurements of intraocular pressure were made with the electronic Schiøtz tonometer (V. Mueller & Co.) and values were expressed according to the 1955 calibration of the Committee on Standardization of Tonometers.

In this study, intraocular pressure of 22 mm.Hg or less in all measurements is considered "controlled", whereas intraocular pressure of 23 mm. Hg or more is considered "uncontrolled". Because some of our patients were losing field at pressures between 22 and 30 mm. Hg in spite of rigorous medical treatment, we considered that intraocular pressure of 30 mm. Hg (as used by Leopold, et al.) was too high to be considered "controlled" for all eyes. Hence, we chose 22 mm. Hg as a level which, if maintained, might prevent further damage.

### 3. Selection of patients

From patients seen in the Glaucoma Consultation Service, Massachusetts Eye and Ear Infirmary, 41 patients known to have glaucoma were chosen for this study:

| | |
|---|---|
| Open-angle | 35 |
| Angle-closure (with or without iridectomy) | 3 |
| Secondary (to P.A.S., following lens extraction) | 3 |
| | 41 |

Of the 41 patients (52 eyes), most were considered uncontrolled; some were considered controlled on their treatment regimen prior to the use of echothiophate; and a few newly discovered cases had not yet been started on treatment.

The uncontrolled group had received intensive medical treatment for glaucoma, in some cases for a year or more, without satisfactory pressure reduction; some of this group demonstrated progression of disc damage and field loss despite rigorous medical therapy. The controlled group had shown no damage or no progression of damage while tensions were running at levels of 22 mm. Hg or under. The untreated group were newly discovered cases.

### 4. Treatment prior to the use of echothiophate

Patients whose glaucoma was considered uncontrolled were receiving maximum or near maximum therapy (that is, four-percent pilocarpine every three hours, 1.8 percent epinephrine bitartrate every six hours often with 0.1 percent DFP at bedtime, and many with Diamox® added in doses varying from 125 mg. every 12 hours to 250 mg. every six hours). Those patients whose glaucoma was considered controlled were on regimens which varied from two-percent pilocarpine every three hours to four-percent pilocarpine every three hours plus 1.8-percent epinephrine bitartrate every six hours; none received Diamox (table 1).

### 5. Administration of echothiophate

It was considered desirable to use the weakest solution of echothiophate which, used as infrequently as possible, would

TABLE 1

Types of glaucoma and adequacy of control prior to study

| Adequacy of Control without Echothiophate | Open-Angle | | Angle-Closure (chronic) | | Secondary to Peripheral Anterior Synechias | |
|---|---|---|---|---|---|---|
| | Patients | Eyes | Patients | Eyes | Patients | Eyes |
| Uncontrolled | 23 | 31 | 3 | 4 | 3 | 3 |
| Controlled | 6 | 7 | | | | |
| Untreated | 6 | 7 | | | | |

achieve and maintain control of intraocular pressure. The drug was used in concentrations of either 0.125 percent or 0.25 percent by topical installation at intervals varying from twice weekly to twice daily. In some cases epinephrine bitartrate 1.8 percent was employed in addition to echothiophate if the latter alone failed to control tension; in other cases Diamox was used in addition to echothiophate for the same reason (but only in those patients taking Diamox on the pre-echothiophate regimen).

In most instances, the topical regimen used prior to echothiophate was continued in one eye, and this treatment was stopped in the eye under test when echothiophate was started. Where Diamox had been used before the study, it was discontinued when echothiophate was started; but if the new drug alone or in combination with epinephrine bitartrate 1.8 percent failed to control ocular tension, Diamox was again added to the regimen.

In the group of newly discovered glaucomas, one eye was started on echothiophate while the fellow eye was started on a regimen of conventional topical antiglaucoma therapy (usually two or four-percent pilocarpine, with epinephrine bitartrate added in some cases).

### 6. Type and frequency of observation

Patients selected for clinical trial of echothiophate were tonographed while receiving their accustomed antiglaucoma therapy. Echothiophate alone was then started in one eye and the treatment regimen in the fellow eye left unchanged. Twenty-four hours after the start of echothiophate, tonography was repeated; thereafter tensions were recorded at weekly intervals for a period of four to eight weeks; the patients were then seen at monthly intervals for a follow-up period of 12 months. The study is continuing.

## II. Results

A. Previously uncontrolled glaucoma eyes (table 2).

B. Previously controlled glaucoma eyes (table 3).

C. Untreated glaucoma eyes. The six cases (seven eyes) previously untreated were all controlled with echothiophate alone, except one eye which was uncontrolled on 0.125-percent echothiophate, 1.8-percent epinephrine bitartrate and Diamox combined.

### 1. Effect of echothiophate on intraocular pressure and facility of outflow

Application of echothiophate to glaucomatous eyes commonly caused a fall of intraocular pressure during the first 24 to 48 hours to levels of 10 to 17 mm. Hg, followed by a rise during the next few days to levels of 16 to 21 mm. Hg, where the pressure remained stabilized. Eyes demonstrating such satisfactory pressure responses also demonstrated improvement in facility of aqueous outflow which usually rose by 0.07 cu. mm./min./mm. Hg or more. Of the 11 eyes whose intraocular pressure was not controlled by echothiophate, five demonstrated a temporary improvement in intraocular pressure associated with increased outflow facility; the remaining seven eyes showed no change in intraocular pressure or facility of outflow. Rate of aqueous flow appeared to be unchanged by this drug.

### 2. Frequency of administration

All eyes whose pressure responded to echothiophate required instillation once daily for satisfactory control. The 11 eyes demonstrating inadequate control under echothiophate therapy were no better controlled by instillation twice daily than by a one-dropper-day schedule.

### 3. Side-effects

No systemic side-effects were noted in our group of 41 patients, nor was there any manifestations of dermatitis. However, allergic conjunctivitis developed at the end of the 10th month in one patient. Discomfort in the form of supraorbital ache, pain local-

TABLE 2

RESULTS OF SUBSTITUTING ECHOTHIOPHATE FOR PREVIOUS MIOTICS

| Previously Uncontrolled | | | Results with Echothiophate | | | | |
|---|---|---|---|---|---|---|---|
| | | | Controlled | | | | Uncontrolled* |
| | | | | Echo. with other Medication | | | |
| Type of Glaucoma | No. of Eyes | Previous Medication | Echo. alone | Epineph. | Diamox | Epineph. & Diamox | |
| Open-angle | 2 | 4% pilocarpine | 1 | | | | 1 |
| Open-angle | 7 | 4% pilo., 1.8% epineph. bit. | 4 | 1 | | | 2 |
| Open-angle | 9 | 4% pilo., 1.8% epineph. bit., and 0.1% DFP | | 3 | 1 | 1 | 4 |
| Open-angle | 6 | 4% pilo., 1.8% epineph. bitartrate and Diamox | | 2 | | 2 | 2 |
| Open-angle | 7 | 4% pilo., 1.8% epineph. bitart., 0.1% DFP & Diamox | 1 | 2 | 1 | 1 | 2 |
| Chronic angle-closure | 2 | 4% pilo. 1.8% epineph. bitartrate | 2 | | | | |
| Chronic angle-closure | 1 | 4% pilo., 1.8% epineph. bitart., & 0.1% DFP | | 1 | | | |
| Chronic angle-closure | 1 | 4% pilo., 1.8% epineph. bitart., & Diamox | | 1 | | | |
| Secondary | 1 | 4% pilo., 1.8% epineph. bitartrate | 1 | | | | |
| Secondary | 1 | 4% pilo., 1.8% epineph. bitart., & 0.1% DFP | | 1 | | | |
| Secondary | 1 | 4% pilo., 1.8% epineph. bitart., 0.1% DFP & Diamox | | | | 1 | |
| TOTAL | 38 | | 9 | 11 | 2 | 5 | 11 |

* Only considered uncontrolled if 1.8% epinephrine bitartrate t.i.d., plus acetazolamide 250 mg. t.i.d., plus 0.25% echothiophate once daily failed to lower tension satisfactorily.

ized to the globe, and transient blurring (one to four hours) was seen in most patients; such discomfort lasted one to seven days, after which no further discomfort was noted despite continued daily application of the drug. Of the 11 patients whose tensions were not controlled by the use of echothiophate, only one complained of discomforting symptoms.

4. EFFECT ON THE NORMAL EYE

Instillation of one drop of 0.125-percent echothiophate in one normal eye (female, aged 35 years) was followed by a marked fall in intraocular pressure (19 mm. Hg to 11 mm. Hg) and a sharp rise in outflow facility. Ocular tension returned to normal in 11 days. Side-effects noted were the same as those mentioned above except that the pain from ciliary spasm was severe. This finding is in agreement with that of Becker,[4] but Leopold, et al.[2] observed no appreciable (greater than 3.0 mm. Hg) fall in intraocular pressure in 27 normal eyes.

TABLE 3

RESULTS OF SUBSTITUTING ECHOTHIOPHATE FOR PREVIOUS MIOTICS IN EYES WITH PREVIOUSLY CONTROLLED GLAUCOMA

| Previously Controlled Cases | | | Results with Echothiophate Alone | |
|---|---|---|---|---|
| Types of Glaucoma | No. of Eyes | Previous Medication | Controlled | Uncontrolled |
| Open-angle | 1 | 2% pilocarpine | 1 | 0 |
| Open-angle | 4 | 4% pilocarpine | 4 | 0 |
| Open-angle | 2 | 4% pilocarpine, 1.8% epineph. bit. | 2 | 0 |
| TOTAL | 7 | | 7 | 0 |

### 5. Observations on stability of echothiophate

Reports[2] have indicated that echothiophate is stable indefinitely when kept at 5°C. Our observations suggest somewhat lower stability. Its effect in lowering intraocular pressure was found clinically to diminish in six weeks despite refrigeration between instillations. This finding prompted a thorough study of the drug's stability by the pharmacy of the Massachusetts General Hospital. Assay for the active material was performed by hydrolyzing test samples with alkali in an atmosphere of nitrogen and then titrating iodometrically the mercaptan formed. Bottles of echothiophate solution were treated as follows:

Group A. Drug kept under refrigeration and unopened.

Group B. Drug kept under refrigeration and the bottle opened once daily.

Group C. Drug kept at room temperature and opened once daily.

| | Percentage of active (nonhydrolyzed) compound | | |
|---|---|---|---|
| | A | B | C |
| Start | 95 | 95 | 95 |
| 2 weeks | | 93 | 90 |
| 4 weeks | | 90 | 83 |
| 8 weeks | 91 | 90 | 76 |

One bottle was refrigerated for five months while unopened and was found to be 64.4 percent active at the end of that period.

In view of the fact that this drug is given on a one-drop-a-day regimen, and since a 0.25-oz. bottle would last over two months, the necessity of refrigerating the bottle seems obvious. It appears that loss of drug potency was probably responsible for some lessening of control of intraocular pressure after four to six weeks of echothiophate treatment in some of our patients.

## III. Comment

Echothiophate lowers intraocular pressure in glaucomatous eyes as Leopold, Gold and Gold reported.[2] For several reasons this drug can be considered a useful adjunct to our medical regimen in the treatment of glaucoma. In the present study it was found to control ocular tension in 12 out of 19 eyes previously uncontrolled on a regimen including DFP. Echothiophate controlled tensions in a few cases in which Diamox combined with other miotics had failed. Despite reports[2] that echothiophate can produce paradoxical elevation of intraocular pressure, no case in this study demonstrated this phenomenon. In this series, echothiophate, with one exception, appeared to eliminate large fluctuations in intraocular pressure, an effect probably related to its long duration of action.

Of the 30 cases which were considered controlled on echothiophate, none showed onset or progression of field loss during 12 months or more of therapy with echothiophate.

No definite conclusions can be drawn in regard to the relative effects of echothiophate on eyes with various types of glaucoma. The results were generally the same in open-angle, chronic angle-closure and secondary (to peripheral anterior synechias following lens extraction) glaucomas.

Echothiophate is not the ideal miotic. It was found to produce side-effects similar to those produced by DFP.[3] Most such reactions lasted only a few days. Blurring of vision noted in a few cases was probably due to pseudomyopia; since blurring was most marked for a few hours after each instillation, it appears desirable that the drug be used at bedtime. Marked miosis was observed (pupillary diameter of one mm. or less) when the 0.25-percent concentration was used; 0.125-percent solutions produced less miosis (pupillary diameter 1.5 to 2.0 mm.). Iris cysts at the pupillary border developed in three cases after three months or more of therapy.

## IV. Summary

A clinical trial of echothiophate has been made in 52 eyes of 41 glaucoma patients for a period of 12 months. It was found to lower

intraocular pressure and improve facility of outflow, thus controlling intraocular pressure, in 27 of 38 eyes in which other intensive medical treatment, including DFP and Diamox in some instances, had failed.

The drug was found to be effective in controlling intraocular pressure in open-angle and chronic angle-closure glaucoma, as well as in glaucoma secondary to peripheral anterior synechias after lens extraction. Echothiophate (0.125 percent) was uniformly effective in controlling intraocular pressure in early, mild cases of glaucoma. In more advanced cases (uncontrolled group in this series) 0.25-percent strength was required.

A merit of echothiophate is its long duration. It has an advantage over DFP in that, unlike DFP and most other anticholinesterase phosphate esters, it is stable enough to be employed in aqueous rather than oil solution, and it is not subject to inadvertent rapid deactivation by exposure to water, as is DFP. Nevertheless, even echothiophate requires refrigeration to retard loss of activity in aqueous solution. At room temperature approximately a quarter of its activity is lost in the course of two months.

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We wish to thank Dr. John Murphy, chief pharmacist, Massachusetts General Hospital, for making possible the tests for stability of echothiophate mentioned herein.

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## Ophthalmic Miniature

If the eye is to be kept turned out, after the operation for internal strabismus, it is done by Mr. Bowman's method. An exceedingly fine thread is drawn through the conjunctiva close to the outer edge of the cornea, and the needle then carried from within outwards, and through the skin at the outer canthus, and the thread secured with plaster on the skin.

Ophth. Hosp. Reports, 1:38, 1857.

# NOTES, CASES, INSTRUMENTS

## BONE FORMATION IN THE TARSAL PLATE*

### ASSOCIATED WITH AMYLOIDOSIS FOLLOWING TRACHOMA

SAMI HAMEED, M.D.
AND
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Frequent references in the literature described amyloid, fatty and hyaline degeneration of the tarsal plate. There are, however, only few reported cases of bone formation of the tarsal plate.

Herbert (1901) reported an interesting case. Stanka (1923) Franklin and Cord (1924), and Wilson (1934) reported bone formation following syphilitic tarsitis, chalazion, and trachoma, respectively.†

The rarity of the condition even in countries where chronic conjunctivitis and trachoma are frequent prompted us to report the following case.

### CASE REPORT

R. D., a woman, aged 55 years, was admitted to the general ward of the Gandhi Eye Hospital because of recurrent redness, irritation, and watering of both eyes for the last 25 years.

On examination it was found that the patient has been suffering from trachoma and its sequellae since childhood. Both upper lids were thickened, due to hypertrophy of the tarsus, and had entropion and trichiasis. There was also senile ectropion of the right lower lid. Both eyes had keratitis, fine corneal opacities, and superficial vascularization. Hypermature cataracts was present in both the eyes. While excising the tarsus during entropion operation of the right upper lid, it was found very much thickened and hard to cut. It was excised as much as possible and the entropion was repaired. The excised tissue was preserved in 10-percent formal saline for histopathologic study.

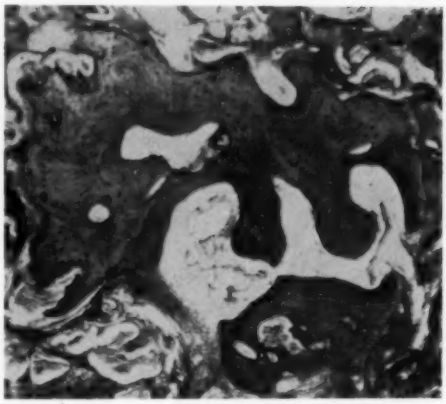

Fig. 1 (Hameed and Nath). Bone formation in the tarsal plate (Hematoxylin-eosin, ×125.)

### HISTOPATHOLOGIC REPORT (figs. 1, 2, and 3)

The section shows six irregular foci of bone formation which stain blue, indicating calcification. It is less lamellated than the normal bone. The lacunae containing cor-

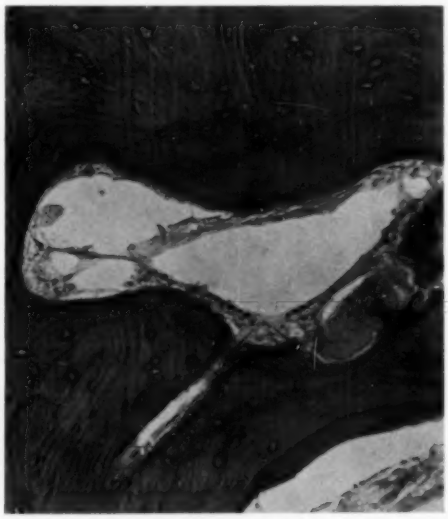

Fig. 2 (Hameed and Nath). Magnification of Figure 1 to show the bony corpuscle in the lamellae and the cavity in the bone which contains fibrous tissue and blood vessels. (Hematoxylin-eosin, ×560.)

* From the Department of Pathology, Institute of Ophthalmology, Aligarh Muslim University.

† All references quoted from Duke-Elder, S.: Textbook of Ophthalmology, London, Kimpton, 1952, v. 5, p. 5007.

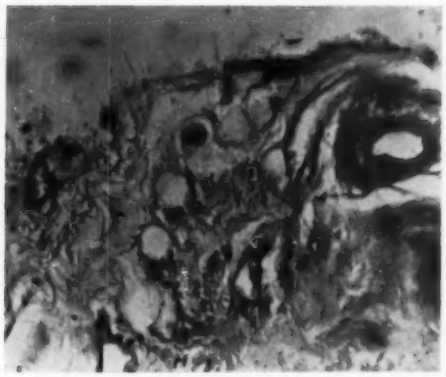

Fig. 3 (Hameed and Nath). Note dark-staining areas of amyloid deposits, especially in the wall of the blood vessels. (Methyl violet, ×125.)

puscles are smaller and more irregular than normal. The canals are defective and scanty. The cavity in the bone is filled with fibrous tissue and blood vessels. Other areas in the tarsal plate, especially the wall of the blood vessels, show amyloid deposits. With methyl voilet staining these deposits show metachromasia.

*Institute of Ophthalmology,*
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## RETINOBLASTOMA*

### With spread by direct continuity to the contralateral optic nerve: report of a case

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That retinoblastoma shows a marked tendency to spread outside the eyeball through the optic nerve of the same eye is well-known and has been widely reported in the literature. But spreading by direct continuity of a retinoblastoma on one side to the meningeal sheaths and optic nerve of the other eye is extremely rare. Bilateral retinoblastoma, which occurs in 20 to 25 percent of cases, seems to be of independent origin.

Merriam,[1] in a series of 17 retinoblastomas with postmortem examination found, in four cases, extension of the tumor to the opposite optic nerve through the chiasm. The tumor cells remained in the subarachnoid space without infiltrating the optic nerve proper. In one of those four cases the tumor extended to the opposite eye and invaded the sclera. Reese,[2] Duke-Elder,[3] Friedenwald,[4] and Salas[5] in an extensive series of 49 cases do not mention this manner of extension of the retinoblastoma.

Weizenblatt[6] published a case of retinoblastoma invasion of the optic nerve of the opposite eye in an eight-year-old white boy. In view of the patient's age and the fact that several pathologists who studied this case in consultation were not convinced that it represented a retinoblastoma (Zimmerman[7]), this must be considered a doubtful instance of the phenomenon which is being reported herein.

In an extensive series of 750 retinoblastomas in the Registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology, Washington, D.C.,[8] there are only two cases. One case showed marked subarachnoid and subdural spread to the opposite eye; the other, a massive subdural hemorrhage in the optic nerve of the opposite eye. Contained within the hemorrhage were many clumps of tumor cells. The subarachnoid space and the stem of the nerve were free of tumor.

### Report of case

L. T. S., a three-year-old girl, was admitted on October 1, 1957, to the General Hospital in Mexico City. When she was two years old, the patient showed a white spot in the right pupil, which extended from the periphery toward the center. Later on the spot acquired a brownish color. Ten days before admission she had vomited repeatedly with subsequent loss of weight. On admission the fundi were explored under general anesthesia, from which the patient never recovered, death occurring the following day. A clinical diagnosis of intraocular tumor of the right eye, probably retinoblastoma, was established.

The autopsy which was performed by Dr. Herman Brandt and Dr. Eugenia Figueroa in the Pathology Unit of the General Hospital, revealed

* From the Service of Ophthalmology, General Hospital. Read at the meeting of the Asociación Mexicana de Patólogos, Mexico City, June 27, 1958.

Fig. 1 (De Buen). Right eye, showing the retro-ocular mass and part of the optic nerve emerging from it. (Gross photograph.)

pulmonary edema and congestion, generalized cyanosis and renal congestion. The only tumor demonstrable was located in the right eyeball and both optic nerves.

*Gross examination* of the eyes and optic nerves showed the right eye to be of firm consistency, measuring 22 by 25 by 21 mm. There was a retro-ocular firm mass, measuring 20 by 20 by 22 mm., involving the recti muscles and the optic nerve with the exception of the extreme posterior portion of the optic nerve (fig. 1). An anteroposterior section of the eye revealed the intraocular structures almost totally replaced by a tumor mass, white-pinkish in color, with irregular hemorrhagic areas and small calcifications (fig. 2-A). A cross section through the retro-ocular mass, 10 mm. behind the sclera, showed the optic nerve to be very thickened, measuring nine mm. in diameter, and similar in color and consistency to the intraocular tumor (fig. 3-A). The posterior portion of the optic nerve along with the chiasm, which were cut longitudinally, showed a similar appearance (fig. 3-B).

The left eye, which measured 21 by 22 by 21 mm. did not show gross changes (fig. 2-B).

*Microscopic examination* revealed a retinoblastoma without rosettes in the right eye, with total replacement of the retina, and wide infiltration of

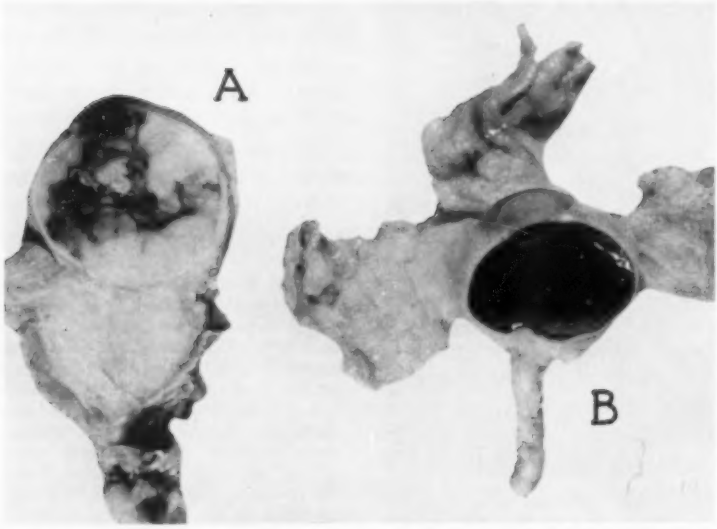


Fig. 2 (De Buen). (A) Anteroposterior section of the right eye. Retinoblastoma occupies almost the total ocular cavity. (B) Anteroposterior section of the left eye showing the normal appearance of the intraocular structures. (Gross photographs.)

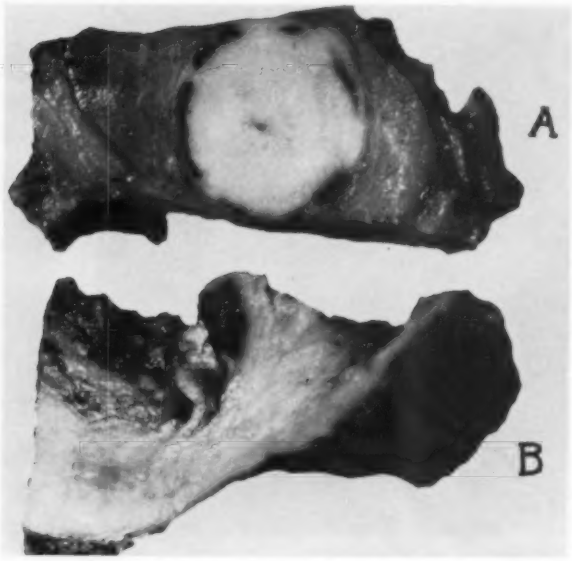


Fig. 3 (De Buen). (A) Cross section of the right optic nerve. (B) Longitudinal section of same nerve with part of the chiasm. These structures are thickened because of the tumor infiltration. (Gross photographs.)

uveal tissues, optic nerve and subarachnoid and subdural spaces as far as the chiasm (figs. 4 and 5).

There were no changes in the left eye, but the subdural and subarachnoid spaces around the corresponding optic nerve were infiltrated with tumor cells from the chiasm to the meningeal cul-de-sac. In addition to this, the superficial part of the optic nerve was infiltrated by tumor (figs. 6 and 7).

Fig. 4 (De Buen). Massive invasion of right eye and optic nerve by retinoblastoma. (Low-power photomicrograph; hematoxylin-eosin.)

## Discussion

When retinoblastoma invades the optic nerve it grows, destroying and replacing the nerve fibers. It may invade the meningeal sheaths and, once this occurs, dissemination into the brain is usual. Retinoblastoma may also give rise to distant metastases which are usually hematogenous (Merriam[1]).

Spreading of the tumor to the opposite meningeal sheaths and optic nerve is extremely rare. The cases reported by Merriam[1] are not illustrated with photomicrographs and those of Paul and Zimmerman[8] (unpublished cases) do not show direct continuity of the tumor along the optic nerve sheaths as clearly as the present case does; also, there was no tumor infiltration of the optic nerve parenchyma on the side opposite the affected eye.

It is important to emphasize that the four cases reported by Merriam and the two cases at the Registry of Ophthalmic Pathol-

Fig. 5 (De Buen). Cross section of right optic nerve in which tumor cells infiltrate the subdural and subarachnoid spaces, totally replacing the nerve tissue. To the right is the cross section of a rectus muscle. (Low-power photomicrograph; hematoxylin-eosin.)

ogy, as well as the present case, were autopsy findings. It would seem that this pathway of extension of retinoblastoma would be demonstrated more frequently if the general pathologist would pay more attention to the postmortem study of the eyes. This might facilitate a better understanding of bilateral retinoblastomas, some of which, due to the lack of adequate and complete studies, undoubtedly are considered to be of independent origin.

It is easy to understand that, if the patient had survived the exploratory procedure and the diseased eye had been enucleated, later

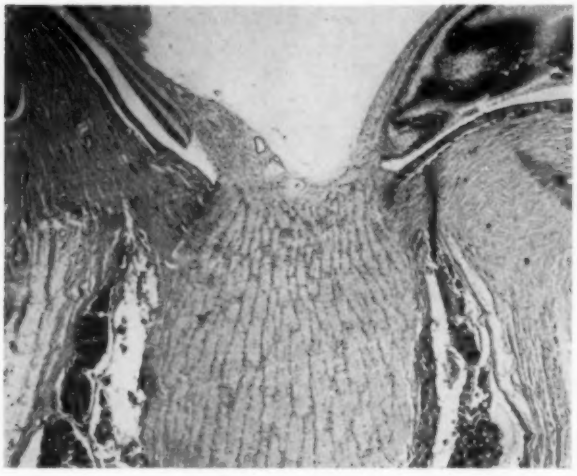

Fig. 6 (De Buen). Posterior portion of left eyeball along with the optic nerve showing the extension of retinoblastoma cells as far as the meningeal cul-de-sac. (Low-power photomicrograph; hematoxylin-eosin.)

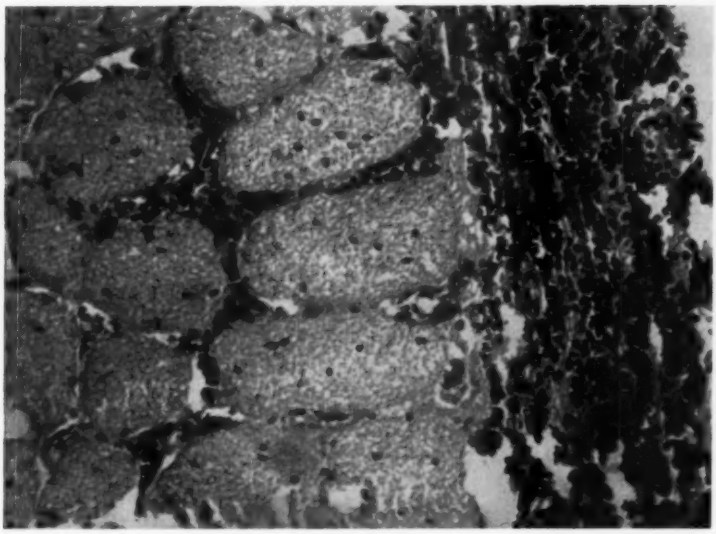

Fig. 7 (De Buen). Cross section of left optic nerve, showing the tumor cell infiltration. (High-power photomicrograph; hematoxylin-eosin.)

on the unaffected eye probably would have been invaded by the tumor, giving the false impression of another case of independent bilateral retinoblastoma.

It is unlikely that the diagnosis of tumor spreading into the optic nerve of the unaffected eye could have been made clinically because the fundus examination would have been negative, due to the lack of intraocular damage. The optic nerve lesion was still minimal, since no retinal changes were demonstrated microscopically.


## Summary

A case of retinoblastoma in one eye with spreading by direct continuity to the meningeal sheaths and optic nerve of the opposite side is reported. Autopsy did not reveal extension of the tumor to the brain or distant metastases.

The necessity of postmortem study of the eyeballs in order to be able to demonstrate more frequently this way of extension of retinoblastoma is discussed.

*Adolfo Prieto 709-10 (12).*


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# SELSUNEF OINTMENT TO TREAT SQUAMOUS BLEPHARITIS

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A novel method of treatment of blepharitis marginalis was described by Cohen* (1954), who used an application of a 25-percent ointment of selenium disulfide every other night for four nights, repeated subsequently if necessary.

Stimulated by this account, a similar course of treatment was started with a selenium sulfide preparation with hydrocortisone. The selenium preparation is marketed under the proprietary name of Selsunef Ointment by Abbott Laboratories.†

The purpose of this note is to review the results obtained by this technique of selenium sulfide treatment in 80 cases during the past 18 months.

## CLASSIFICATION OF CASES

Table 1 shows the age and sex distribution of the cases reviewed. The number suffering from concurrent seborrhea of the scalp is also given. It is noted that the number of males greatly exceeds the number of females in both the uncomplicated cases of blepharitis marginalis and those associated with seborrhea capitis.

Table 2 gives a classification of cases according to the severity of symptoms. The criteria adopted are similar to those of Cohen: (1) Mild, consisting of scaliness only; (2) moderate, scaliness and redness; (3) severe, as under (2) but also loss of some lashes; (4) very severe, as under (3) but complicated by keratitis.

TABLE 2

CLASSIFICATION ACCORDING TO SYMPTOMS

| Symptoms | Male | Female | Total |
|---|---|---|---|
| Mild | 12 | 8 | 20 |
| Moderate | 20 | 16 | 36 |
| Severe | 15 | 6 | 21 |
| Very severe | 3 | — | 3 |
| TOTAL | 50 | 30 | 80 |

## METHOD OF TREATMENT

The method of treatment consists of the application of Selsunef on the affected eyelids with a glass spatula, after all scales have been removed. The ointment is gently rubbed down to the eye lashes with the spatula and the lid is massaged gently. The ointment is left on for half an hour and then removed with dry cotton wool. The frequency of treatment initially tried was every other day for 10 consecutive sessions. With this mode of treatment 10 consecutive applications proved, however, often insufficient and the routine was later changed to 10 daily applications. This proved quite satisfactory.

Concurrently with this treatment, the patients were advised to instil a mild antiseptic or astringent solution three times a day for

TABLE 1

DISTRIBUTION OF PATIENTS STUDIED

| Age (yr.) | Number of Patients Treated | | | No. of Cases with Seborrhea Capitis | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| 5–10 | 3 | 5 | 8 | — | 1 | 1 |
| 10–20 | 8 | 5 | 13 | 3 | — | 3 |
| 20–30 | 9 | 10 | 19 | 4 | 5 | 9 |
| 30–40 | 18 | 4 | 22 | 6 | — | 6 |
| 40–50 | 11 | 4 | 15 | 1 | — | 1 |
| 50–60 | 1 | 2 | 3 | — | 1 | 1 |
| TOTAL | 50 | 30 | 80 | 14 | 7 | 21 |

* Cohen, L. B.: Am. J. Ophth., **38**:560, 1954.

† Selenium sulfide (0.5 percent) with hydrocortisone acetate (0.5 percent) in a soft petrolatum base.

the duration of the treatment and for one month after its termination. Also, a nightly rubbing of the eyelids with hydrocortisone (one percent) with neomycin (0.5 percent) ointment, for the same length of time, was prescribed.

A month after the termination of Selsunef treatment, the patient was re-examined and, if the condition of the eyelids proved satisfactory, all treatment was discontinued and the patient was told to reattend only if the scales on the eyelids reappeared.

No severe side-effects were noted during treatment. However, great care was always taken not to introduce any of the ointment into the conjunctival sac. In one case, where the patient administered Selsunef himself, contrary to medical advice, a rather severe keratitis promptly developed. This contrasts strongly with Cohen's experience. The keratitis responded well to orthodox treatment.

A few patients complained of a burning sensation but this subsided after the first four or five applications. Examination by slitlamp revealed no signs of keratitis and, later, hydrocortisone drops were given to these cases and relief was immediate.

## Results

Up to the time of writing, 80 patients have been treated within the past 18 months, all of whom had been previously treated by various methods, invariably unsuccessfully. However, a few patients had shown some regression under previous treatment for as long as treatment was continued. Three of the patients had suffered for some time from severe blepharoconjunctivitis with recurrent keratitis.

Of the 80 cases treated, 21 were also affected by seborrhea capitis. Contrary to the findings of Cohen, it is felt that there is some association between blepharitis marginalis and seborrhea, that is, some of the cases with both scalp and eyelids affected showed improvement of blepharitis marginalis when the scalp only was treated. Conversely, some of the cases when treated only for blepharitis marginalis often relapsed, and treatment proved successful when the scalp was also treated. It was therefore decided to treat the seborrhea, too, if this condition was present. Scalp treatment consisted of the application of Selsun suspension, as recommended by the makers (Abbott Laboratories).

TABLE 3
Results of treatment

| Condition | Total | Cured | Relapsed |
|---|---|---|---|
| Mild | 20 | 20 | — |
| Moderate | 36 | 28 | 8 |
| Severe | 21 | 15 | 6 |
| Very severe | 3 | 2 | 1 |
| Total | 80 | 65 | 15 |

Table 3 summarizes the results of treatment in all cases. Every case responded to treatment but some relapses were observed, mainly in the group having concurrent untreated seborrhea of the scalp. These cases cleared after combined treatment of scalp and lids. Four cases had more than one relapse but symptoms during relapses after treatment tended to get milder and quiescent periods longer.

Of the 80 cases, four were followed for more than one year; others, between four and 12 months.

## Summary

Eighty cases of blepharitis marginalis treated with Selsunef are reviewed. Improvement was general. A technique of treatment is described. Some association between blepharitis marginalis and seborrhea capitis was found. The danger of introduction of Selsunef into the conjunctival sac is stressed.

*3, D'Israeli Street.*

I should like to thank Abbott Laboratories for the supply of Selsunef.

# KERATO-ACANTHOMA

## Report of two cases

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Myer Medine, M.D.
and
A. J. Orfuss, M.D.
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Kerato-acanthoma or molluscum sebaceum is a benign tumor of the skin. It resembles squamous-cell carcinoma of the skin both grossly and microscopically. The differentiation rests on the clinical rather than on microscopic features. Rapid growth and spontaneous involution characterize the lesion. It is usually single but occasionally multiple. It appears chiefly on exposed areas and has been noted at times on patients working with petroleum products. Predisposing factors, such as blistering sunburn, long-continued exposure to tars and shale oil, and arsenic intake, vary in the different case reports or are completely lacking. A tempting virus etiology, while strongly supported by an otherwise extensive parallel between these conditions and verrucae, cannot be ascertained, since inoculation experiments so far have failed to reproduce the disease.

The concept that tumorlike keratoses of Poth,[1] primary self-healing squamous-cell epithelioma of the skin,[2] and kerato-acanthoma,[3] are variants of the same disease is steadily gaining ground.[4] Rapid development, benignity, and spontaneous involution with scarring and typical pathology are common to all three types of tumors. There are, however, a number of divergent elements in the three entities which have to be elucidated before this theory can be recognized as final.

On the other hand, familial incidence is present only in the primary self-healing squamous-cell epithelioma of the skin. The face is the usual site for kerato-acanthoma, which develops as a single lesion, grows to the largest size, and occurs usually in the fifth or sixth decade of life. These distinctive features are a help in establishing the diagnosis for each variety, should varieties still be recognized.

Two cases, one involving the left upper lid, and the other the inner canthus of the right eye prompts this report.

### Case reports

#### Case 1

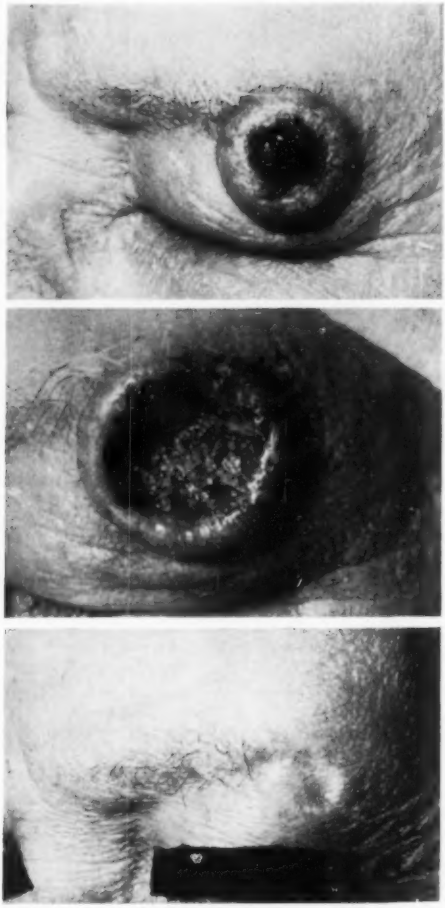
A white man, aged 57 years, a signal operator for a railroad, developed a small boil-like lesion in the left eyebrow. Intramuscular penicillin failed to heal the lesion. When first seen eight weeks after the onset the appearance was as seen in Figure 1. The tumor was round, 25 mm. in diameter, involved the major part of the lateral half of the upper eyelid, and restricted lid movement. The border was sloping, hard and yellowish-white in color. The top, six mm. above the base, was flat and covered with a dry solid brown crust. The tumor was not tender and could be easily moved. The surrounding skin was not infiltrated. No palpable lymph nodes were evident. The lesion did not change in size during four weeks of observation.

The patient's history was negative for skin tumors, acne, or boils. He had been an out-door switch operator for over 20 years, and the trains had been diesel-engine driven. He presented a healthy rosy complexion.

After the covering crust was lifted, a crumbly semisolid amorphous material was found. Histologic preparation showed the material to consist almost entirely of masses and whorls of lamellated keratin and parakeratin; in a few areas there were rounded groups of degenerated prickle cells, clotted blood was also noted, no molluscum bodies were seen. As the next step, the central mass was removed, exposing a deep crater (fig. 2).

Report of the histologic examination of a segment through the raised border reads as follows:

"The walls are lined by irregular-shaped masses of pseudoepitheliomatous squamous cells which bear a remarkable resemblance to a bonafide Grade I squamous-cell epithelioma. The tumor cells are well differentiated and form thick interwoven bands, within which intra-epithelial collections of neutrophils and a few keratin pearls are seen. An intensive chronic inflammatory reaction is present in the adjacent stroma. The hyperplastic squamous cells fill the corium and undergrow the overlying surface epidermis. The cells extend directly to the lateral border of the specimen. The history of rapid growth and unusual clinical presentation, plus the high degree of tumor-cell differentiation would be most unusual in a squamous-cell epitheloma. These find-



Figs. 1, 2, and 3 (Givner, et al.). (Top) Appearance of patient eight weeks after onset. (Middle) After removal of the central mass. (Bottom) Lateral third of eyebrow was lost. (Courtesy A.M.A. Arch. Dermat., Kallas, A.: 78:207-209, Aug., 1958.)

Fig. 4 (Givner, et al.). Histologic section from the border of the growth. (Courtesy A.M.A. Arch. Dermat., Kallas, A.: 78:207-209, Aug., 1958.)

ings, however, are characteristic of this kerato-acanthoma, which histologically is often confused with an epithelioma." (fig. 4.)

Curettage and fulguration of the growth yielded no lasting improvement; the border regrew to its previous height in eight days, and the central depression began to fill anew. Podophyllin[5, 6] has been used with good results in kerato-acanthoma. Accordingly, the whole lesion was treated with applications of podophyllin (25 percent) in benzoin tincture once every two weeks over a period of 12 weeks. Great care was used not to get this into the conjunctival sac as a serious keratitis would have resulted from the mixture. The response to the treatment was most gratifying from the start. The border of the lesion shrank gradually and disappeared, and the central part became epithelized. Finally, a depressed atrophic area surrounded by an overhanging, slightly indurated edge remained. The eyebrow was lost in its lateral third (fig. 3). The patient has been under observation two years without any sign of recurrence.

CASE 2

Mr. S. O., aged 35 years, presented himself on January 6, 1955, with a round infiltrated, elevated, slightly erythematous nodule of the inner canthus of the right eye measuring 0.75 inch in diameter. This had been present for two months (fig. 5). There was a central depression covered with a hemorrhagic crust. This had been present for two months. The central crusting had reappeared repeatedly upon removal. No pain or constitutional symptoms had been present. No regional adenopathy was present. A pinch biopsy was done under Novocaine. The report was as follows:

"The epidermis is mildly irregularly acanthotic. The corium reveals a diffuse cellular reaction with fibroblasts and polymorphonuclear leukocytes present. The vessel walls were thickened."

After dermatologic consultation with Gustav Weissberg, a diagnosis of kerato-acanthoma was made.

The lesion was injected with Novocaine, desiccated, and curetted repeatedly, then dressed with bacitracin ointment. By February 5th the lesion had healed (fig. 6).

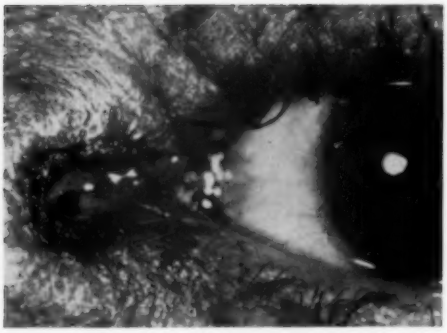


Fig. 5 (Givner, et al.). Kerato-acanthoma of the inner canthus.

Fig. 6 (Givner, et al.). Healed lesion of inner canthus.

### Comment

It is felt these cases should be reported since, from 1936 when MacCormac and Scarff[7] first established this tumor as a clinical entity, only one case report appeared in the ophthalmologic literature, that of Christensen and Fitzpatrick.[8]

By bearing this entity in mind, unnecessary surgery and worry can be obviated, as about 20 percent of tumors formerly diagnosed as squamous-cell carcinoma turned out to be kerato-acanthoma.[9]

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## OPTIC NEURITIS*

### Evaluation of treatment with retrobulbar hydrocortisone

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Rapid and favorable clinical improvement in the appearance of the optic disc and early restoration of vision can be obtained by the retrobulbar injection of hydrocortisone-acetate solution in cases of optic neuritis.

Several reports in the current literature confirm the beneficial results obtained with steroid therapy in the treatment of acute inflammations of the posterior segment of the eye. Favorable results were obtained by Woods[1] and by Gordon, et al.[2] with the parenteral administration of corticotropins in cases of optic neuritis. More recently fav-

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orable clinical response has been obtained by prednisone given orally. The current literature on the use of cortisone therapy in all fields of ophthalmology is voluminous but few workers have reported about its efficacy when used retrobulbarly in cases of optic neuritis.

## Case reports

### Case 1

Mr. P. Singh, aged 23 years, was admitted on January 12, 1959, with complaints of bilateral deterioration of vision to perception of light only.

On January 4th he experienced mild pain in the right eye while working in the office as a typist and a little while later experienced sudden diminution of vision in the right eye to hand movements only. Two days later vision in the left eye also deteriorated to the perception of light only. On the day of admission vision was hand movements only in both eyes.

He had had injections of procaine penicillin (four lac. units once daily) for five days since the onset of the complaints but with no relief. Never had he had headaches or ocular pain. His past history did not reveal any possible clue to the disease.

External eye examination showed both eyes normal. Pupils were almost of normal size but the reaction to light was very sluggish. Intraocular pressure was normal. Vision in both eyes was perception of light only.

*Ophthalmoscopic examination* of both eyes showed clear media. Discs were markedly congested and elevated to two to three diopters. The disc margins were hazy and ill defined and in the surrounding retina the veins were edematous and slightly engorged. No exudates or hemorrhages were seen. The rest of the fundus appeared normal.

*Fields* could not be taken at this stage due to the poor vision. Dignosis of optic neuritis was made on the basis of the ophthalmoscopic findings and the marked visual loss.

*Systemic examination* did not reveal anything abnormal. The neurologist could not discover any demyelinating process. Blood pressure was 130/80 mm. Hg.

*Laboratory investigations.* Total white cell count 7000/c.mm. Differential leukocyte count showed: Polymorphs, 78 percent; lymphocytes 21 percent; monocytes 1.0 percent. E.S.R. was 7.0 mm. one hour. Urine was negative for sugar or albumin. Blood for Kahn's test was negative. Skiagram of the posterior group of sinuses including the sphenoidal sinuses revealed nothing abnormal. Cerebrospinal fluid pressure was normal. On qualitative examination, the cell count, sugar, chloride, and protein contents were within normal limits. Screening chest films showed normal lung fields.

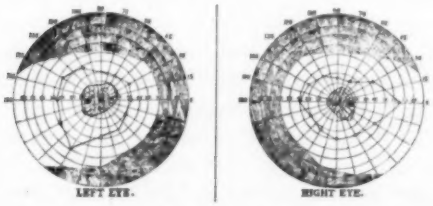


Fig. 1 (Sharma, Kulshrestha and Nath). *Case 1.* Visual fields taken on January 15, 1959.

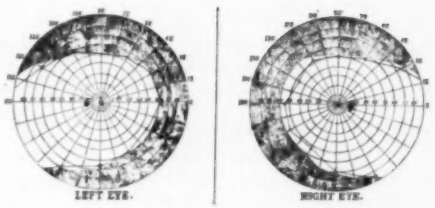


Fig. 2 (Sharma, Kulshrestha and Nath). *Case 1.* Visual fields taken on February 10, 1959.

Treatment was commenced on January 12, 1959. An injection of 1.0 cc. of hydrocortisone acetate (25 mg./cc.) was given retrobulbarly in both eyes. The retrobulbar injections were repeated on every third day to a total of six injections in each eye.

There was marked subjective improvement in vision after the first injection. In 24 hours, vision was finger counting in each eye at 0.5. On January 15th, peripheral fields with 3/330 white and central fields with 1/1000 white showed marked generalized peripheral constriction of the field with a central scotoma with some enlargement of the blindspot. (fig. 1).

After the ninth day of treatment (January 20th), after three retrobulbar injections in each eye, the fundus picture was nearly normal, although the vision was still poor as shown in Table 1.

On February 10th, his distant vision was 6/9 in each eye and J1 for near. Both peripheral and central fields were now normal (fig. 2). Optic discs also appeared normal. The patient came for check up again on May 2nd and the findings were the same (fig. 2).

### Case 2

Mr. A. Razak, aged 25 years, was admitted on December 24, 1958, with very poor vision in the left eye. Since December 22nd, he had noticed marked sudden diminution of vision in his left eye. Past history did not reveal anything.

*External eye examination.* Both eyes appeared normal. The pupil in right eye was normal with brisk reaction to light. The left pupil appeared semidilated but the reaction to light was normal. Vision was: R.E., 6/6; L.E., finger counting at six inches.

*Ophthalmoscopic examination.* R.E. showed mild hyperemia of the optic disc but the disc margins were well defined. Veins were slightly congested. The rest of the fundus appeared normal.

TABLE 1

VISUAL FINDINGS IN CASE 1

| Date 1/13/59 | 1/15/59 | 1/20/59 | 1/25/59 | 1/30/59 | 2/6/59 | 2/10/59 |
|---|---|---|---|---|---|---|
| R.E. finger counting 0.5 m. | 2/60 | 6/60 | 6/36 | 6/24 | 6/12 | 6/9 Near J1 |
| L.E. finger counting 0.5 m. | 2/60 | 6/60 | 6/24 | 6/18 | 6/9 | 6/9 Near J1 |

TABLE 2

VISUAL FINDINGS IN CASE 2

| Date | 12/24/58 | 12/25/58 | 12/26/58 | 12/29/58 |
|---|---|---|---|---|
| Vision L.E. | Finger counting at 6 in. | 6/60 | 6/24 | 6/12 partial |

L.E. showed marked congestion of the optic disc. Disc margins were very much blurred and could not be defined. Slight edema of the optic disc and the surrounding retina was noted. Veins were slightly engorged. No hemorrhages or exudates were seen. The rest of the fundus appeared normal. Media were clear.

Both perimetry and Bjerrum's screening showed normal fields in the right eye but these tests could not be performed in left eye due to poor vision.

Diagnosis of optic neuritis in left eye was made on ophthalmoscopic examination and markedly poor visual acuity.

*Systemic examination* did not show anything abnormal. Blood pressure was 116/74 mm. Hg.

*Laboratory investigations.* Urine was negative for sugar and albumin. Total white cell counts, 7800/per c.mm. Differential leukocyte counts: polymorphs 72 percent, lymphocytes 25 percent, monocytes, 3.0 percent. E.S.R. 11 mm./one hour. Kahn's test was negative.

Skiagram of posterior group of sinuses (sphenoidal) was normal. C.S.F. pressure was normal. Qualitative C.S.F. examination did not show any abnormality. Screening chest films showed normal lung fields.

Treatment was commenced on December 24th; one cc. of hydrocortisone acetate solution (25 mg. per cc.) was injected retrobulbarly in the affected eye every other day. There was marked improvement in vision in left eye as shown in Table 2.

Perimetry was done on December 29th and showed normal fields with 3/330 mm. white. Bjerrum's screening was also normal (fig. 3).

On December 29th, the fundus examination showed a normal appearance of the optic disc. Disc margins were clear cut and well defined. Veins were slightly congested.

The patient left against medical advice on the same day before completion of the full treatment and did not come for any follow-up.

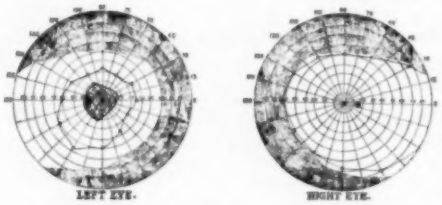


Fig. 3 (Sharma, Kulshrestha and Nath). *Case 2.* Visual fields taken on December 25, 1958.

## COMMENTS

The results in these two cases were highly satisfactory. Vision improved in a few days from mere perception of light to 6/9 both eyes in one case and in another from finger counting at six inches to 6/12, partial, in the affected eye.

The number of cases in this series is, of course, too small for statistical analysis, but the marked improvement observed the day after start of treatment with retrobulbar injections was so dramatic as to rule out any purely spontaneous remission of the disease.

Bayet, et al.[3] also reported beneficial results with retrobulbar injection of hydrocortisone in six cases of optic neuritis and marked improvement in vision in four cases.

It is our belief that the retrobulbar use of hydrocortisone did materially contribute toward rapid restoration of good vision in our two cases and its use undoubtedly is a valuable addition to the therapy of optic neuritis of diverse etiologies. It appears advisable to start the retrobulbar hydrocortisone treatment without undue delay and without waiting for necessary investigations of the case.

*S.M.S. Medical College Hospital.*

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## A MODIFIED PRINCE RULE

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This new Prince rule was designed to enable the examiner to make simple direct readings of accommodation near-point and convergence near-point, respectively, without having to worry about computations which often prove inaccurate and unreliable. The familiar Prince rule was found unsatisfactory for different reasons. With this older rule one must keep track of the imaginary position of the anterior focal point in front of the cornea as the accommodation near-point landmark. One must also keep in mind the imaginary position of the PcB (baseline connecting the centers of rotation of the eyeballs) behind the cornea as the zero position from which to compute the near-point of convergence. Also, the rule is placed clumsily and obliquely either at the side of the bridge of the nose or on the cheek, depending on the examiner's habits.

The inexactness in the design and operation of the common Prince rule is shown in two separate conflicting statements in manuals issued by the Air Force[1] and the War Department.[2] In one of the manuals the instruction reads: "The zero point on the rule should be placed 15 mm. from the cornea." In another manual the instruction reads: "The end of the Prince rule, or a modification of the same, is placed edge up at the side of the nose 11.5 mm. in front of the anterior surface of the cornea."

It would seem obvious that in neither instance could any technician or examiner ever locate a true or even approximate imaginary position 11.5 mm. or 15 mm. from the cornea merely by touching the side of the bridge of the nose, without even making due allowance for the variable nose prominences in different persons.

My accommodation and convergence near-point rule has been bifurcated so as to rest evenly and symmetrically on both cheeks rather than obliquely on an uncertain nose position. A side view of the head will show that this contact point on the malar prominences is fortunately and usually in vertical alignment with the anterior surface of the cornea.

In about 10 percent of examinees I have found an error of up to plus or minus 3.0 or 4.0 mm. which can be due to variable soft tissue thickness. This is too slight to affect the reliability in the readings for accommodation or convergence near-point. With such a fairly constant landmark one can make necessary allowances on this new rule for accommodation near-point and for convergence near-point tests respectively.

The direct readings on the accommodation portion of the rule allow for a landmark setting of the anterior focal point 11.5 mm. in front of the cornea. The zero position in the convergence section of the rule is calibrated for a position 13.5 mm. behind the anterior surface of the cornea which usually happens to be in vertical alignment with the malar prominence on the cheek.

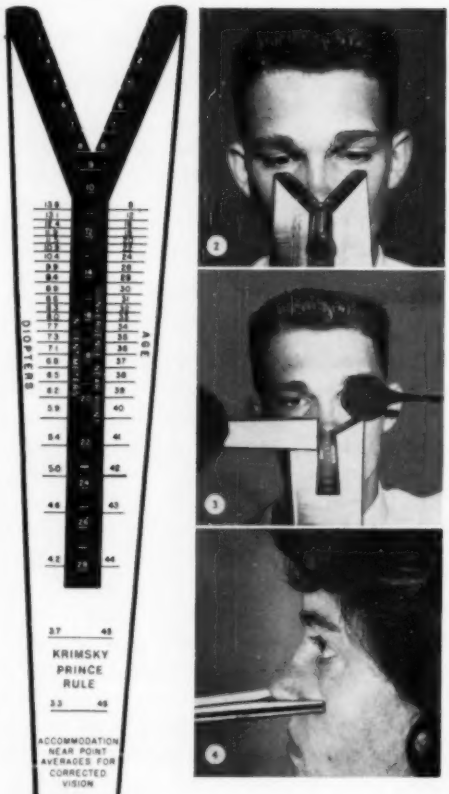
Incidentally, with such symmetric contact of a bifurcated bar on both cheeks I am now engaged in studies to ascertain the feasibility of substituting this landmark for the established one used in routine exophthalmometry, namely, the front of the outer orbital margin. With a properly designed instrument resting on the malar prominences one should be able to measure proptosis, exoph-

thalmos, and enophthalmos, as well as to compare the status of each eye respectively.

Some years ago[3,4] I designed an instrument for the critical measurement of convergence and accommodation near-points in which I utilized a "sliding or telescopic cheek rest . . . and . . . the anterior pole of the cornea is used as a fixed guide for such measurements and is observed through a window on each side of the bifurcated bar . . . having vertical hair lines which the examiner aligns with the anterior surface of the cornea."

My new rule presents a broad platform which enables one to make individual tests for near-point of convergence as well as for separate testing of accommodation near-point for each eye respectively. Because the bar is bifurcated to rest on both cheeks simultaneously one does not have to move the rule from one cheek to the other as in the Prince rule. The median portion of this bifurcated rule is delineated for convergence near-point testing with its readings already compensated for PcB. On either side of the median convergence ruled section one finds accommodation near-point readings for the right and the left eyes respectively in relation to age. These readings are also compensated to allow for the anterior focal point, thereby enabling one to make direct readings.

Convergence near-point is tested with an object moved gradually along the median section of the rule toward the eyes or rather the bridge of the nose.[4] The rule is supported firmly against both malar prominences by means of a handle held by the subject. I find a pencil flashlight more desirable than using a beaded pin because one's attention is thereby aroused. Furthermore, the positions of the corneal light reflexes can be critically observed to ascertain whether or not they remain in their normal pupillary positions as the examiner brings the light nearer to the eyes. As soon as one eye gives way and turns out, the limit of convergence near-point is said to have been reached. In that eye the corneal light reflex is displaced




Figs. 1 to 4 (Krimsky). (1) Full-length view of Krimsky-Prince rule. (2) Eyes focused on flashlight over medial portion of rule for testing convergence. (3) Right eye looking at accommodation test card; left eye covered. (4) Edge of rule placed against malar prominences of cheeks; note vertical alignment with anterior surface of cornea.

inward from the normal pupillary position as the eye turns out. This provides objective evidence of the exact distance of the convergence near-point. This reading is then noted and recorded in mm. "A near-point of convergence (pc) greater than 70 mm. is a cause for rejection for pilot applicants falling into classes I and II. Candidates for flying training will not be allowed to wear corrective lenses while being tested for near-point of convergence."[5]

TABLE 1

ACCOMMODATION NEAR-POINT READINGS (IN DIOPTERS) FOR RESPECTIVE AGES

| Age (yr.) | Normal | Minimum Acceptable for Air Force |
|---|---|---|
| 17 | 11.8 D. | 8.8 D. |
| 18 | 11.6 | 8.6 |
| 19 | 11.4 | 8.4 |
| 20 | 11.1 | 8.1 |
| 21 | 10.9 | 7.9 |
| 22 | 10.7 | 7.7 |
| 23 | 10.5 | 7.5 |
| 24 | 10.2 | 7.2 |
| 25 | 9.9 | 6.9 |
| 26 | 9.7 | 6.7 |
| 27 | 9.5 | 6.5 |
| 28 | 9.2 | 6.2 |
| 29 | 9.0 | 6.0 |
| 30 | 8.7 | 5.7 |
| 31 | 8.4 | 5.4 |
| 32 | 8.1 | 5.1 |
| 33 | 7.9 | 4.9 |
| 34 | 7.6 | 4.6 |
| 35 | 7.3 | 4.3 |
| 36 | 7.0 | 4.0 |
| 37 | 6.7 | 3.7 |
| 38 | 6.4 | 3.4 |
| 39 | 6.1 | 3.1 |
| 40 | 5.8 | 2.8 |
| 41 | 5.4 | 2.4 |
| 42 | 5.0 | 2.0 |
| 43 | 4.5 | 1.5 |
| 44 | 4.0 | 1.0 |
| 45 | 3.6 | .6 |

Note: Diopter values computed by dividing near-point in inches into 40 or in centimeters into 100.

In my rule the accommodation near-point readings for comparable ages (table 1) remain the same as in the older Prince rule in order to adhere to accepted standards. The dioptric scale lists average accommodation near-point readings for respective ages based on emmetropia or on fully corrected refractive errors. Abnormalities in the position of the accommodation near-point are noted for each eye separately. Any small card is used for the uncovered eye to recognize print while the fellow eye is covered. From a near position this card is gradually moved farther away until the print is discernible. This position is then noted or marked with a wax pencil on the rule. Testing is then transferred to the other eye and another reading is noted. If, for example, the accommodation near-point reading for a 20-year-old subject is five diopters of accommodation instead of the normal 11.5 diopters one assumes that there is a loss of 6.5 diopters of accommodation. Such loss of accommodation should make one think of one of several possibilities, namely, hyperopia, or paralysis of accommodation due to injury or paralysis of the ciliary muscle. If the near-point reading for a 30-year-old subject is 13.1 diopters instead of the normal average of 8.9 diopters one thinks of myopia or of spasm of accommodation.

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## INFLAMMATORY GRANULOMA OF THE IRIS

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In 1953 an interesting problem, noteworthy from the point of view of general pathology, was discussed by A. Fuchs, who described 10 cases of unusual and rare proliferations in the iris. Ernst Fuchs, who had published seven cases of this kind, considered these proliferations to be hemangiomas which had been present before enucleation. In all his cases severe inflammation was

present; four were due to corneal ulcer, three cases to injury. The eyes were enucleated on the average of 14 days after the beginning of the disease. He did not consider that the severe inflammation was the cause of this newly formed tissue for the following reasons:

1. In acute inflammation no new tissue is formed within the iris itself, only a membrane on the surface.

2. Tissue in inflammation shows a juvenile character, being composed of fibroblasts and many leukocytes, so different in character from the tissue described.

3. This tissue is quite similar in all the cases discussed and is localized in the same place in the iris in spite of the different appearance which inflammation of the iris has in different cases. Therefore, E. Fuchs concluded that this tissue had nothing to do with the inflammation. The fact that this tissue was found by accident only in inflamed eyes is explained by noting that it is usually inflamed eyes which come to enucleation and anatomic examination.

Ernst Fuchs considered these nodules to be vascular tumors because so many vessels and so many large nuclei are present in the tissue. He called them nevus vasculosus and classified them among the telangiectasias, a subdivision of angiomas. They entered into the literature as such and Gilbert (von Graefe-Saemisch's Handb. Gesam. Augenh., 1939) gives an accurate description of them.

A. Fuchs, on the contrary, expressed the opinion that these proliferations, appearing as nodules or small dispersed endothelial growths, are real inflammatory granulomas. In his 10 cases, he found the nodules combined with purulent iritis and has never found a similar nodule in a globe with a normal anterior segment.

These granulomas bear a certain relation to the granulation tissue which is found when a prolapsed part of the iris is starting to be transformed into a staphyloma of the cornea. The staphyloma does not develop from connective tissue originating in the cornea but from that formed by the iris. In the tissues of the iris which become very edematous by prolapse, a larger amount of newly formed vessels, mostly solid endothelial tubes, are formed. Such tissue can be seen in Samuels and Fuchs, *Clinical Pathology of the Eye*, Plate 11/2.

I found such a case among the slides of the Eno Laboratory of the New York Eye and Ear Infirmary. It is evidently the first case of this rare pathologic change found in America and merits description. (Subsequently, I found another such change in a study set which I had received from A. Fuchs and shall briefly describe this slide later in this paper.)

## Case report

### Case 1

*Clinical history.* A man, aged 71 years, was first seen in the clinic on September 15, 1950. He gave a history of loss of vision, left eye, for four days. Examination showed a markedly inflamed eye with a hypopyon ulcer of the cornea and absence of light perception. Enucleation was advised.

*Pathologic description.* There is a perforated ulcer in the center of the cornea and the defect (five mm.) is filled with fibrin, red blood corpuscles, and pus cells. Anteriorly, the defect extends over the perforation and we find here a loose tissue of fibroblasts and edematous corneal lamellae covered by epithelium. On one side an infiltration of leukocytes and necrosis of the posterior layers are found; behind lies much pus. The posterior layers of the opposite side of the ulcer are much less infiltrated. The endothelium has disappeared to a large extent around the perforation. The posterior surface of the cornea is covered by some red blood corpuscles and loose pigment.

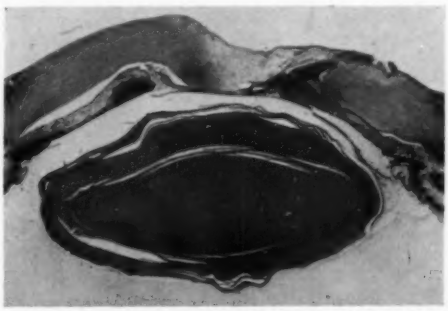

Fig. 1 (Samuels). *Case 1.* Granuloma of the iris after perforation of corneal ulcer (×17).

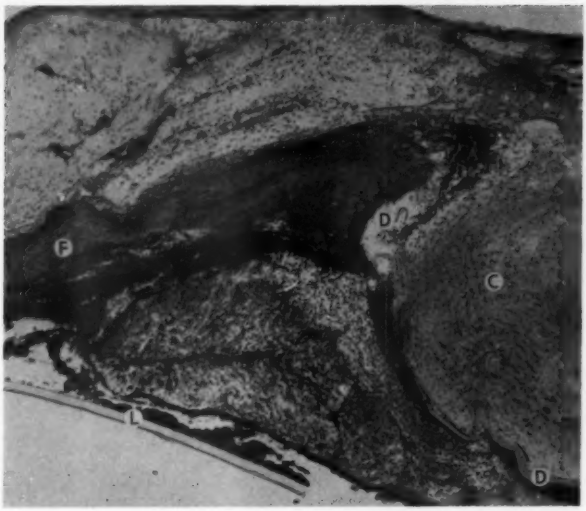


Fig. 2 (Samuels). *Case 1.* (C) cornea, (D) Descemet's membrane, (F) fibrin filling the perforation, (L) lens capsule (×105).

The filtration angle is slightly obliterated on one side. The anterior chamber is nearly obliterated due to the perforation and what remains is filled with blood and fibrin. The lens lies against the perforation opening and is covered by some pus and blood cells, and on one side by loose pigment.

On one side the pupillary portion of the iris has fallen into the perforation opening and is somewhat swollen. Loose pigment has extended over the anterior face of this pupillary portion. The sphincter is covered by a massive, red-stained proliferation of tissue which is sharply defined against the other tissue of the iris. Behind the sphincter less of this tissue is found, although peripherally a nodule is seen. This tissue is composed of numerous endothelial tubes filled with blood together with a large amount of endothelial cells which are massed together, along with some leukocytes and pigment particles.

Quite similarly but to a less degree endothelial proliferation is found on the other side of the pupil in front of the sphincter. Proliferated endothelial tubes are also present near the root of the iris. Here, also, the dilator has proliferated and is infiltrated with some leukocytes.

A real endophthalmitis septica is not present because there is no considerable exudate upon the detached ciliary body. Likewise, in the vitreous behind the ora serrata there are a number of necrotic and partly living leukocytes which later on would have become augmented and would have formed a vitreous abscess if the eye had not been enucleated. The papilla participates in the inflammation by a very insignificant periphlebitis. The retina shows only isolated leukocytes on its inner surface.

CASE 2

*The clinical history* states that there was a perforating injury with an iron object one month ago. The eye subsequently developed an hypopyon, lens abscess, beginning endophthalmitis, and was enucleated.

*The pathologic examination.* The cornea shows a perpendicular perforating wound near the center with the epithelial edges approximated and a downgrowth of epithelium halfway along each cut edge with pus cells between these downgrowths. The lower half of the corneal wound shows scar formation with retraction of the posterior edges. There is adhesion at this point of the fibrinous mesh which is present, along with a marked proliferation of leukocytes in the anterior chamber. There has been a perforation of the lens capsule with an anterior lens abscess.

The iris shows a diffuse infiltration of pus cells, and at the pupillary area and again at the base, there is a granulomatous proliferation of the kind described previously. These areas are composed mainly of eosin-staining endothelial cells with indistinct borders and large oval nuclei and here, too, are clearly visible endothelial tubes filled with blood—

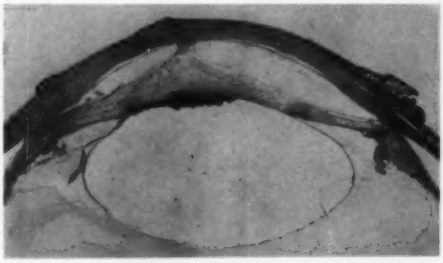

Fig. 3 (Samuels). *Case 2.* Granuloma of the iris after perforating injury of cornea (×17).

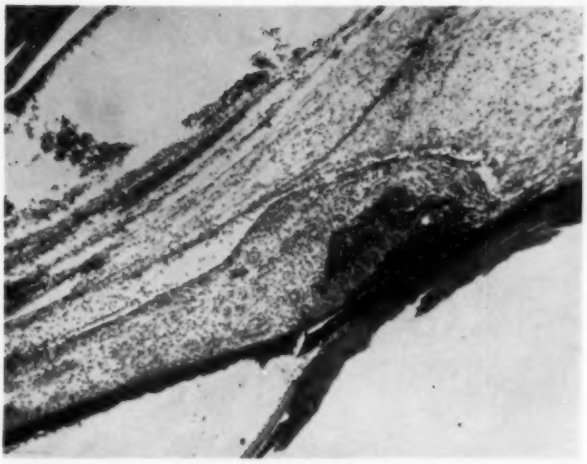

Fig. 4 (Samuels). *Case 2.* Pus cells in the anterior chamber, lens cortex, granulomatous nodule of the iris.

analogous to the granulation tissue we see in a prolapsed iris.

## Comment

Besides a similar microscope appearance, the two globes have in common the fact that both were found in cases with injury and purulent iritis.

If we compare the changes in the iris of these cases with those of E. Fuchs and A. Fuchs, we realize immediately that they are identical. The excellent colored pictures in the paper by A. Fuchs correspond closely to the findings in these slides. Furthermore, these cases show the same relation to purulent iritis that A. Fuchs emphasized, and seem to substantiate his opinion about the inflammatory etiology of these proliferations.

## Summary

The tissue of the iris has little tendency to proliferate in the absence of inflammation. There is a rather rare type of proliferation of cells in the iris wherein endothelial cells may form small aggregations all over the stroma (endotheliosis). Endothelial cells may also form nodules of varying size. Ten such cases were described by A. Fuchs. These nodules were mostly present in the pupillary portion, on either side of the sphincter or pervading it. E. Fuchs presented seven cases of such nodular formations as nevus vasculosus. I have described two cases which I believe identical to those of these authors. The fact that these nodules were all found in cases in which purulent iritis was present demonstrates that they are inflammatory granulomas, since no such nodules have been found in normal eyes. Apparently these granulomas disappear later if the acutely inflamed eye is not enucleated, for they are not found in atrophic eyes or in those with staphylomas.

One point is of especial interest. A. Fuchs mentioned a certain analogy of the tissue of these granulomas and the changes of tissue in recent prolapsed irises. In my first case less endothelial proliferation is seen on the side where the iris was not prolapsed and a large nodule is seen in the iris situated in the corneal perforation. Since in all the reported cases a corneal perforation was present, it seems likely that the perforation and the hypotension which resulted, at least for some time, play a role in the proliferation of the endothelium and the formation of the granuloma.

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# TUMOR OF ORBIT*

## Metastatic from malignant bronchial adenoma

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and
Walter G. Sawchak, M.D.
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This patient manifested a generalized malignant metastatic involvement, including the orbit, without any symptomatology whatever aside from periodic definite proptosis and chemosis of the eye. How this could exist without in some manner producing some need for relief is difficult to understand. Had it not been for orbital symptomatology it appears that this patient might have avoided any physical examination that would have disclosed the pathologic condition present.

A search of the literature fails to disclose any similar report, though many reports detail metastasis to the eye direct from the lesion in the bronchi. It was only after a prolonged study by the pathology service in this case that the final diagnosis was established.

### Report of case

V.C.H., aged 38 years, a white woman, was first seen in the ophthalmology clinic at the Veterans Admistration Hospital on April 7, 1958, with a complaint of repeated attacks of pain and swelling of the left eye, and double vision. This began Christmas Eve, 1957. She was put on hot packs, with some improvement. The swelling recurred. She consulted a local physician who treated her for allergy. After using eyedrops the eyes became more aggravated. Her visual acuity was 20/20 and she read four-point type.

Examination revealed a marked edema of the upper anl lower lids of left eye, completely closing the eye. The conjunctiva was chemotic. The cornea and anterior chamber were clear. The nervehead was normal. The vessels were normal. There were no hemorrhages or exudates. There was no extraocular muscle impairment. The pupils were equal, reacted well to light and accommodation. The sinuses transilluminated well. No nasal discharge was present. The tonsils were absent. There were four central porcelain-capped teeth.

During the process of examination, 10-percent Neosynephrine solution was used to obtain pupillary dilation. There soon occurred a noticeable reduction in the swelling of the lids and conjunctiva. A diagnosis of allergic blepharochalasis was made. X-ray films of sinuses and teeth were requested. Neosynephrine (10 percent) and Chlortrimeton were given and the patient was requested to return on April 14th for further observation.

On this date the swelling was markedly reduced. A very small spongelike mass was now felt in the lower orbit along the outer third of the inferior orbital ridge. The mass could be palpated along the floor of the orbit. There was no impairment of ocular motion. An orbital cyst or pseudogranuloma was suspected. X-ray films showed some increased density at the outer angle. No evidence of erosion was visible. The sinuses were normal. In view of the almost complete subsidence of the swelling no further treatment was recommended.

She returned to the out-patient clinic on May 14, 1958, with a recurrence of the previous swelling, in addition to double vision. Visual acuity was R.E., 20/20; L.E., 20/60.

There was a marked swelling of both upper and lower lids of left eye, with marked chemosis of the conjunctiva. The left eye was considerably proptosed. The mass in the left infraorbital region was now markedly enlarged and firm. There was a paresis of the left external rectus muscle. She was admitted to the hospital with a diagnosis of tumor, left orbit, proptosis of left eye, and paralysis of left external rectus muscle (fig. 1).

On May 16th the swelling was again markedly decreased. She had been on Cortisone and Neosynephrine for several days.

Pelvic examination by the staff physician and the consultant revealed an extremely indurated cervix with possible parametrial fixation. The uterus was slightly enlarged. Cultures from the conjunctival sac showed hemolytic Staph. aureus. Blood examination was normal. X-ray films of the chest showed a large number of small nodular infiltrations in both lungs consistent with a metastatic malignancy. There was some haziness along the bony structure of the left orbit. No sensitivity to PPD,

Fig. 1 (Kulvin and Sawchak). Preoperative marked swelling of left upper and lower eyelids. No conjunctival exudate.

* From the Veterans Administration Hospital, Coral Gables, Florida.

Fig. 2 (Kulvin and Sawchak). Tumor tissue is seen in stroma, with fibrosis of surrounding stroma. The squamous epithelium is intact, with no invasion. (Cervix, ×65.)

histoplasmin and coccidioidomycosis was obtained.

A biopsy from the cervix, taken on May 21, 1958, by the staff surgeon showed intact squamous epithelium covering dense fibromuscular tissue which was infiltrated by numerous nests of polygonal and pleomorphic tumor cells. No keratinization was seen. There were tumor cells in the lymphatic and vascular spaces (fig. 2). A diagnosis of infiltrating epidermoid carcinoma of cervix was made. A radioisotope examination on May 21, 1958, indicated active proliferating tissue adjacent to the left globe.

An exploratory procedure was made through the lower lid and a fairly large mass was enucleated by finger dissection. It was found to extend along the floor of the orbit to the apex, invading the floor and the lateral wall of the orbit. The entire mass could not be removed; apparently it infiltrated into the lateral and inferior sheaths of the globe.

The histologic report showed large masses of fibroblastic connective tissue interspersed with large areas of necrosis and small foci of calcification. Nests of epidermoid-appearing cells with atypical nuclei were scattered throughout, as were lymphocytes and large histiocytes. All this indicated a metastatic epidermoid carcinoma, with fibrosis and necrosis (fig. 3).

Irradiation was first given to what was considered the primary site, the cervix region, and not to the eye at this time. The proptosed eye receded completely, leaving a slight bagginess of the lower lid at the site of the exploratory procedure (fig. 4). The paralysis completely cleared up, with recovery of vision. No intraocular changes were noted at any time. The patient was discharged June 16, 1958, to return daily for five weeks of X-ray therapy to the pelvis. During this period it was felt that, since the proptosis had, it seemed, been treated adequately by surgery no X-ray therapy, in addition to that given to the pelvis, was needed. During this period the patient noticed an occasional spotting of bright red blood in the stool.

On September 4, 1958, the patient was readmitted because she had had a tremor of the left leg followed by a grand-mal seizure. In the admission office she again had a left leg tremor followed by a grand-mal seizure. Physical examination was not changed from the previous admission except for slight brawny discoloration of the lower abdomen. She later became lethargic, with development of increasing motor weakness of the left arm and leg, incontinence and low-grade fever due to urinary infection. She went steadily downhill and died on September 19, 1958.

### Autopsy findings

Internal examination showed multiple tumor masses in many organs. The lesions in the lungs were gray-white to mottled, and firm; they varied from 0.5 cm. to 5.0 cm. in diameter, and were most prominent in the hilar areas, especially on the right. A 2.0 cm. rough, mottled, gray, firm tumor elevated the mucosa of the right middle lobe bronchus and projected approximately 0.5 cm. into

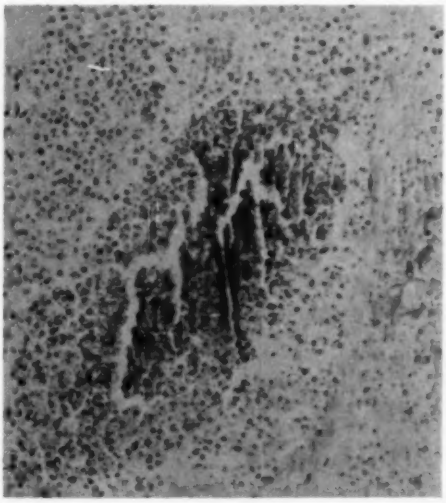

Fig. 3 (Kulvin and Sawchak). Original retrobulbar biopsy, showing necrosis and fibrosis of tumor and adjacent tissue (×65).

Fig. 4 (Kulvin and Sawchak). Following exploratory procedure and removal of tumor mass from inferior temporal aspect of left orbit. About four weeks after operation. Residual bagginess of eyelid. Proptosis markedly reduced.

the lumen (figs. 5 and 6). Similar masses of tumor were present in the right lobe of the liver (fig. 7) and in both kidneys; minute submucosal nodules were seen in the cervix. The thyroid contained small nodules on its periphery which grossly appeared to be normal thyroid tissue. A 2.0 cm. cystic, red, granular tumor mass occupied the right frontal white matter; similar lesions were present in the right parietal subcortical white matter, in the posterior portion of the right temporal lobe, and in the left cerebral and right cerebellar hemispheres (fig. 8). The pituitary was enlarged but grossly uninvolved by tumor. The base of the skull posterior to the left orbit showed a small area of erosion. Permission for further eye examination was not granted.

The tumor was identical histologically in

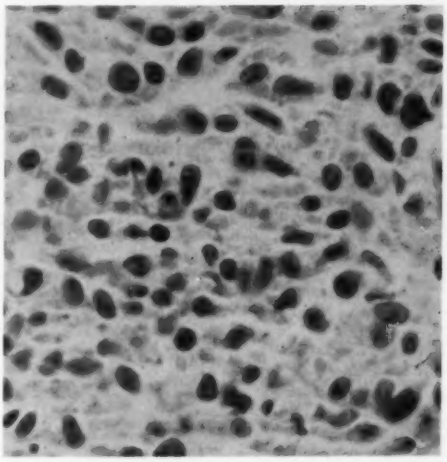

Fig. 6 (Kulvin anl Sawchak). Tumor shows abundant cytoplasm, with variation of nuclear size and staining characteristics. Cytoplasm was markedly eosinophilic. (Lung, ×312.)

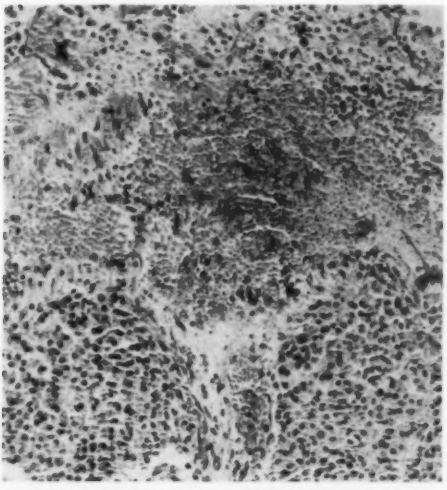

Fig. 5 (Kulvin and Sawchak). Tumor with areas of necrosis which invades the parenchyma but does not destroy the epithelium of the bronchus above. (Lung, ×65.)

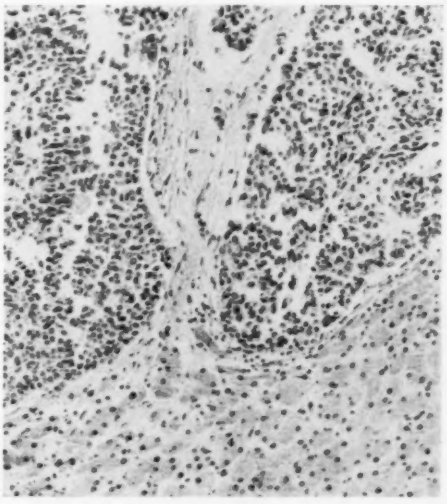

Fig. 7 (Kulvin and Sawchak). Two areas of tumor, with intervening band of fibrosis invading liver. (Liver, ×65.)

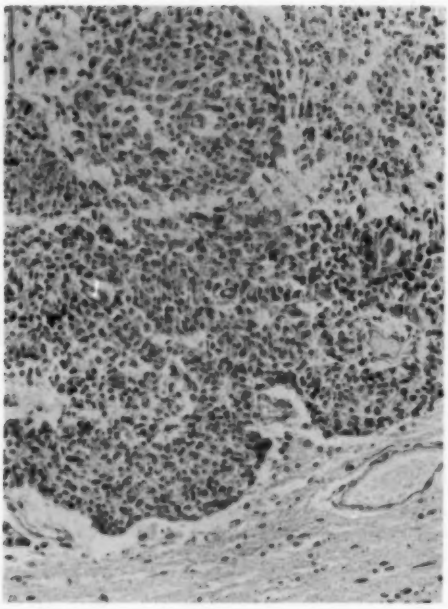

Fig. 8 (Kulvin and Sawchak). Tumor invading the brain shows looser arrangement of cells. (×65.)

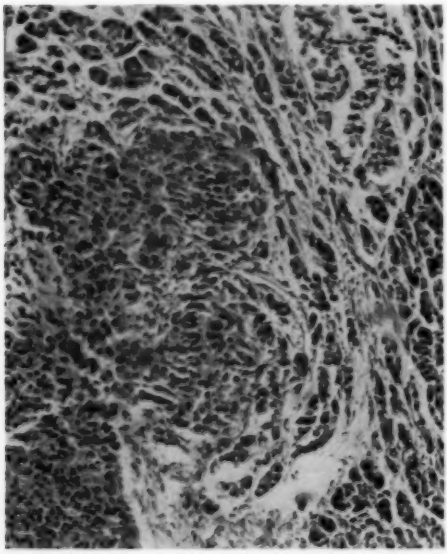

Fig. 9 (Kulvin and Sawchak). Area of invasive tumor on left, with normal pancreas and islet of Langerhans on right. Tumor cells have deeply eosinophilic cytoplasm. (×65.)

all sites, and consisted of varying sized nests without an organoid pattern. The nuclei were ovoid, polychromatic, variable in size, and surrounded by a distinctly eosinophilic cytoplasm. Mitoses were not abundant. In the lung, kidneys, liver and pancreas (fig. 9) nests of tumor were separated by varying sized bands of dense fibrous tissue. Central necrosis was prominent, and in the uterus (fig. 10), cervix, and kidneys, areas of calcification were conspicuous. The small nodules seen in the thyroid histologically proved to be tumor. In the brain, the islands of tumor cells were similar to those seen elsewhere but were looser and more edematous. The tumor mass described in the right middle lobe bronchus was microscopically elevated but did not originate from the bronchial mucosa. The bronchial glands were not involved by tumor. Re-examination of the earlier retrobulbar and cervical biopsies showed histologically similar tumor. The cervix revealed no involvement of mucosa and the retrobulbar tissue showed advanced necrosis in an histologically identical cancer. The final diagnosis was metastasizing malignant bronchial adenoma.

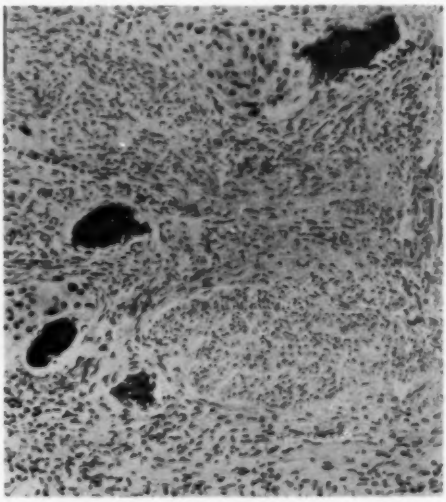

Fig. 10 (Kulvin and Sawchak). Tumor of myometrium, with fibrosis, necrosis and calcification. (Uterus, body, ×65.)

## Discussion

It is significant that the pathologists are reluctant to diagnose malignancy arising from a bronchial adenoma. Controversy has developed whether there is carcinomatous degeneration of an adenoma or actual invasion. Moersch[1] says that no metastases occur in adenoma of bronchi. On the other hand, Goldman[2] states that finding bronchial adenoma in conjunction with multiple tumors of low-grade malignancy in other organs suggests that the stimulus for production of bronchial adenoma is capable of producing neoplasms in other organs.

Rabin and Neuhof[3] think that the adenoma is a clinicopathologic entity. Remote metastases are extremely rare. Jackson and Konzelman[4] also found no evidence of metastases.

Goldman[5] states that bronchial adenoma comprises a group of histologically different tumors of epithelial origin usually located in a stem or lobar bronchus. They are slow growing and rarely metastasize. Considerable scrutiny and controversy surround the malignant nature of these tumors.

Metastatic orbital tumors, as noted by Duke-Elder,[6] presumably are rare because of the difficulty encountered by blood-borne emboli in entering the right-angled bend from the internal carotid artery to the ophthalmic artery. Similarly the direct origin of the left common carotid artery from the aortic arch may account for the predilection of metastatic deposits for the left side.

Metastasizing malignant bronchial adenoma is blood borne. Deposits may be multiple in one orbit, or bilateral, and assume the histologic characteristics of the parent growth. These metastases usually appear as late as a year after the primary tumor has developed. The preferred site is one or more of the orbital muscles. An early symptom, therefore, is diplopia which results when function of the involved muscle is impaired by pressure from the invading tumor; muscular contraction may be impaired by a spreading local cancerous lymphangiitis. Frequently the tumor lies in the muscle cone and, in this position, produces diminution of vision associated with edema around the nervehead; these may be early symptoms.

The striking feature in the clinical aspect of the case herein reported was the apparent complete lack of manifestation of any general symptomatology that might have suggested a primary lesion. Reese states that not infrequently the metastatic focus in the eye manifests itself before the primary site is discovered. However there were no orbital lesions involved, all lesions being intraocular.

As for treatment of such a lesion, Lederman[9] feels that, if the patient's general condition is satisfactory, an orbital metastasis should be treated by radiotherapy. If this is not done the patient may live long enough to develop the distressing symptoms associated with progressive and uncontrolled proptosis and his terminal state may become truly wretched. Secondary deposits of this type respond reasonably well to radiotherapy.

*70 N.E. Second Street (32).*

Photographs from the Department of Medical Illustration, Veterans Administration Hospital.

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## ANTHRAX OF THE EYELID

NOEL T. SIMMONDS, M.D.
*Alexandria, Louisiana*

L. O. H., a white man, aged 37 years, an agriculture teacher, consulted me on March 2, 1945, complaining of swelling and itching of the upper eyelid, giving a history of vaccinating cattle with a live anthrax vaccine during the previous week. The appearance was that of angioneurotic edema of the upper eyelid. The following day, a small pustule was opened on the upper lid. The next day I was out of my office so he consulted his family doctor who hospitalized him. Total white count was 10,500 with 64 segs. Urine was normal. The swelling continued and on the following day, which was the fourth day after he consulted me, black necrotic spots began to develop on the upper eyelid, making the diagnosis evident. He was given large doses of penicillin and sulfadiazine; rather rapid improvement followed. When he was admitted to the hospital, his temperature was only 99°F. This was on the third day after consulting me. On the fourth day it was over 100°F. and on the fifth day was 103°F. On the sixth day when the diagnosis was made and penicillin and sulfadiazine started, temperature was 103°F. and dropped rather rapidly to normal within 72 hours. Three-plus albuminuria was present on the ninth hospital day, with an occasional red and white cell and sulfa crystals.

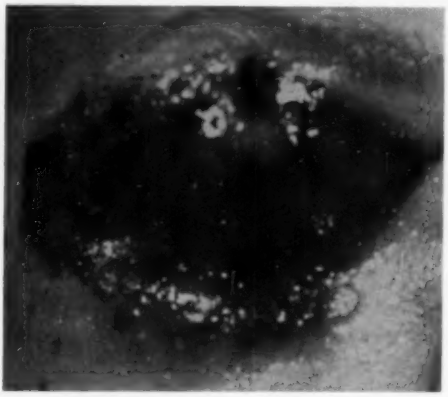

Fig. 2 (Simmonds). Seventh day after consulting me.

Cultures were of Staphylococcus aureus only. However, examinations of scrapings

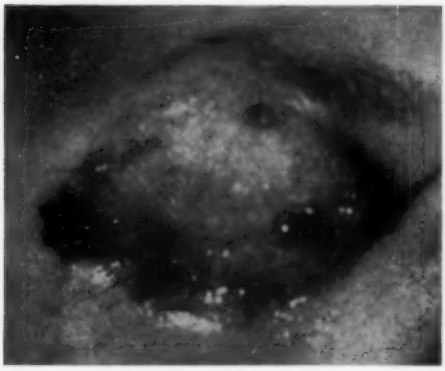

Fig. 1 (Simmonds). Fifth day after consulting me.

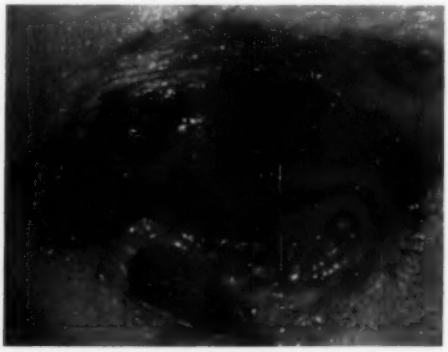

Fig. 3 (Simmonds). Fourteenth day after consulting me.

Fig. 4 (Simmonds). Twenty-first day after consulting me. Slough excised in office after patient went home.

revealed a very "large bacillus resembling anthrax."

### Comment

Diagnosis of anthrax usually depends on the history of handling animals or hides and the development of gangrene, as well as identifying the bacillus from scrapings or culture. This man probably inoculated himself by accidentally wiping his eyelids with live vaccine. The same type of live vaccine is still in use today.

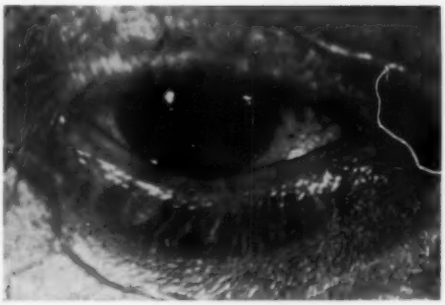

Fig. 5 (Simmonds). End-result, good functioning eyelids and satisfactory cosmetic appearance.

*1300 Jackson Street.*

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## GENERAL ANESTHESIA

### For ophthalmic surgery in children

Paul Kushner, M.D.
*Brooklyn, New York*

A specialty hospital offers the anesthetist a rare opportunity to concentrate upon and to perfect techniques and to accumulate data in a limited field of surgery. At our hospital we have developed a method of managing our pediatric eye patients which we have found highly successful and which has enjoyed a high degree of acceptance by the ophthalmic surgical staff. Our method comprises no departure from standard techniques or equipment, and is readily applicable to other fields of surgery although we have found it particularly suitable to pediatric ophthalmic surgery. This report is not presented with the intention of establishing the efficacy of this technique to the exclusion of others. During the accumulation of the data we have encouraged informed discussion and have no doubt that other methods in other hands are equally worthy, as honest critics both within and outside the hospital have demonstrated. We do feel that the results of our experience with more than 1,000 consecutive cases deserves reporting.

Our experience leads us to believe that all pediatric patients undergoing eye surgery should be intubated. We have now adopted this as a standard procedure and we deviate from it only where specific contraindications to intubation exist. These are few and rare. Our critics have been most vociferous on this point, and we concede that intubation is not mandatory for many of the operative

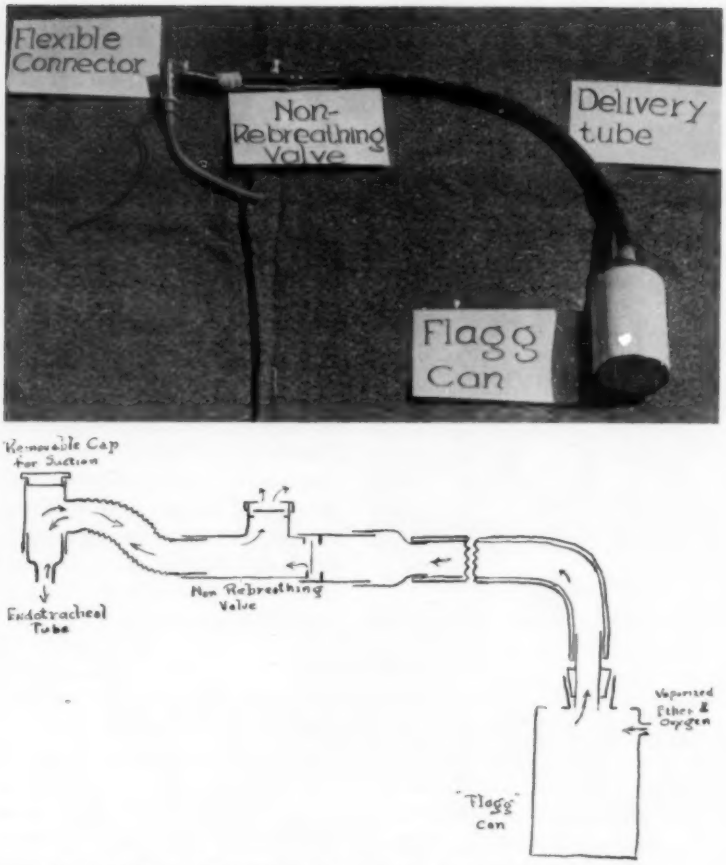


Fig. 1 (Kushner). The mechanical setup for the apparatus used in general anesthesia for ophthalmic surgery in children.

procedures but is nonetheless highly desirable.[1,2]

When the sterile operative field is no more than a few inches from the airway and would be difficult to approach in an emergency, we have found that intubation has produced smooth, uneventful, and uninterrupted anesthesia. This is especially appreciated during intraocular surgery. When coughing or squeezing is not only bothersome but could contribute to the loss of contents of the globe, the endotracheal tube is more than a convenience; it contributes to performance of the surgical procedure and the patent airway assures the patient a greater margin of safety.

The mechanical setup is illustrated in Figure 1. Essentially, it is a modification of the technique of Flagg.[3] The endotracheal adaptor is connected through a flexible connector to a nonrebreathing valve, then through a delivery tube to a "Flagg can." Vaporized ether and oxygen are fed into the Flagg can from any standard anesthesia apparatus. The patient inhales the anesthetic mixture from the can but exhales to the atmosphere via the nonrebreathing valve. The position of the nonrebreathing valve in the system

minimizes the accumulation of carbon dioxide, a vital factor in the conduct of smooth pediatric anesthesia.

Although the majority of children in this study were admitted for extraocular muscle surgery, the series includes a fair representation of pediatric ophthalmic surgery from an unselected group of patients. The distribution of patients by procedure follows:

| Procedure | Percent |
|---|---|
| Extraocular muscle surgery | 74.0 |
| Cataract surgery | 6.5 |
| Traumatic injuries of globe (repair) | 4.5 |
| Tumors of the orbit (all types) | 5.0 |
| Ptosis operations (all types) | 2.0 |
| Plastic repair of lid | 1.6 |
| Iridectomy | 1.2 |
| Enucleation | 1.2 |
| Repairs of canaliculi | 1.0 |
| Tumors of the globe (all types) | 1.0 |
| All others | 2.0 |

The patients in this group range in age from nine weeks to 16 years, the upper limit being arbitrarily chosen. All patients were premedicated with Meperidine and atropine in dosage appropriate to the patient's constitutional requirements. The dosage of atropine prescribed has been moderately increased over the quantities customarily used in general surgery to compensate for the reflex bradycardia which results from the surgical manipulation of the ocular adnexae.[4,5] It should be noted here that this complication is not unexpected since the vagal reflex is particularly active in this adolescent age group[6] in which the vagal blocking effect of atropine is highly desirable.

The younger patients were induced with divinyl ether by open drop, the older patients with nitrous oxide and oxygen in a semiclosed system. All were carried and maintained with ether and oxygen alone. All intubations were accomplished without the use of relaxants so the results could be attributed to the technique and agents used.

The endotracheal tubes were of the soft plastic variety of appropriate diameter and of a length chosen so that they would protrude no more than two cm. below the cords. We use plastic tubes because the flexible character of the plastic tends to conform more readily to the posterior pharyngeal curve with less likelihood of causing irritation by pressure.

Since the endotracheal tube serves only as an airway we use no cuffs on the tubes and their "short" length obviates the possibility irritating the carina. Under these circumstances the patient breathes through, as well as around, the endotracheal tube. This leak in the system, though somewhat extravagant, does not detract appreciably from adequate maintenance control of the agent; and avoiding inflated cuffs has considerably reduced the number of postoperative complications.

One of the most encouraging features of the study has been the low incidence of operative complications. We have noted, as have others[4-7] that bradycardia occurs frequently, though not consistently, during traction on the extraocular muscles. This is such a common observation that we do not interrupt the surgery unless the rate falls below 60 beats per minute. Removing the muscle hook or relieving the tension on the muscle or the globe is usually all that is required to restore a more normal rate.

In one patient we observed a fall in rate to 12 beats per minute; releasing the tension on the muscle and ventilation with oxygen promptly restored the pulse to normal rate and the surgery continued without event. In another, the rate fell to 15 beats per minute and the patient developed gallop rhythm. This patient also responded promptly to similar management. Subsequent investigation revealed that this patient had a congenital heart deformity not recognized preoperatively. These were the only serious operative complications encountered in the series of 1,000 cases.

Except for occasional suction and adjustment of apparatus the surgery has been uneventful. Postoperatively we have had six cases of laryngeal edema, all presumably due to intubation, for an over-all incidence of 0.6 percent. In none of these was the intubation deemed difficult or traumatic, and

all recovered within 48 hours with no treatment other than steam inhalation and antibiotics.

In addition to low incidence of complications, the method has much to recommend it. It allows the anesthetist maximum control of the airway with a minimum of apparatus about the face, thus minimizing interference with the activities of the surgeon. This makes it ideally suitable for ophthalmic surgery. Frequently, the requirements for the surgery are no more than analgesia for the patient, and a quiet field for the surgeon. This is particularly so in extraocular muscle surgery. With this method, light planes of anesthesia are easily and evenly maintained, and yet the method is flexible enough to meet those situations where deeper anesthesia is required.

This method also keeps the anesthetist away from the surgical field but still in control and still able to cope quickly with unforeseen emergencies. The "Flagg can" serves as a monitor through which the anesthetist can listen to the breath sounds throughout the procedure. Although only one group of anesthetic agents is studied here, it is felt that other agents could be employed with equal success.


## Summary

A simple method of managing pediatric anesthesia for ophthalmic surgery is described. The results of this method in a series of 1,000 cases are discussed.


*2000 Kings Highway (29).*

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## Ophthalmic Miniature

Many optometrists refer a patient for cataract surgery only when the cataract has reached a fairly mature point in its development. Others never refer a patient for cataract surgery as long as one eye has good enough vision to take care of the patient's visual demands.

H. Kaplan,
Am. J. Optometry and Am. Acad. Optometry, **36**:517, 1959.

# OPHTHALMIC RESEARCH

EDITED BY FRANK W. NEWELL, M.D.
950 East 59th Street, Chicago 37, Illinois

Abstracts of papers presented at the meeting of the Southeastern Section of the Association for Research in Ophthalmology, Inc., at The Medical College of Georgia, Augusta, Georgia, December 5, 1959.
Winston Roberts, *Section Secretary*

**Evolution and development of new instruments for corneal grafting.** Richard G. Weaver, M.D., Department of Ophthalmology, Bowman Gray School of Medicine, Winston-Salem, North Carolina.

A series of Kodachrome slides and movie film strips were presented to show the early evolution and development of several new instruments and techniques for corneal grafting. The first of these instruments was a unit to do penetrating corneal grafts. The unit was designed to fix the peripheral cornea and central corneal button with suction to prevent collapse of the anterior chamber so that the button could be removed with one cut of the trephine. The instrument was designed so that the trephine would fit into the two areas delivering suction as a piston to prevent loss of the anterior chamber. The second set of instruments was designed to mechanize the preparation of a mushroom or step-corneal graft. These instruments were designed so that the graft was prepared endothelial-side up with the endothelial surface of the central penetrating portion of the graft protected at all steps. These instruments are in a state of development and the final design has not been attained.

**Congenital toxoplasmosis: VI. Expected versus observed incidence of the disease.** John R. Fair, M.D., chief, Ophthalmology Division, Department of Surgery, The Medical College of Georgia.

Many cases of congenital toxoplasmosis go unrecognized because only the eyes are seriously involved. The frequency and importance of the congenital infection are thereby underestimated. An accurate determination of the incidence of congenital toxoplasmosis is necessary because of its connection with the problem of recurrent chorioretinitis in older children and adults.

In the general population, a gradual increase in the frequenecy of positive skin tests for toxoplasmosis is noted in the younger age groups. As many as one third to one half of all older adults show serologic evidence of past infection. This suggests that congenital toxoplasmosis should be much more frequent than is commonly thought. The gap between the expected and observed incidence of the disease has been closed considerably by the recognition of those cases in which clinical evidence of the infection is limited to the eyes.

Chorioretinitis is such a constant feature of congenital toxoplasmosis that it may be used as an index in case finding. In the study being reported, general hospital patients and prenatal outpatients were skin tested for toxoplasmosis. At the same time, the oculi fundi were examined through widely dilated pupils. Each age group was well represented in the total of 679 cases. Ten individuals with old healed chorioretinitis were found. Of these, one case was obviously due to congenital syphilis. In two cases, no etiology could be determined. On the basis of history, clinical findings and serologic tests, two cases were assumed to be due to acquired toxoplasmosis. In the remaining five there was presumptive evidence that congenital toxoplasmosis was responsible for the chorioretinal scars.

The number of cases involved is too small to be significant but the results indicate that such a method might be profitably employed on a larger scale as one means of attempting to determine the true incidence of congenital toxoplasmosis.

**Morphologic and histochemical changes occurring in cat corneas during long-term glycerol freezing.** F. W. Stocker, M.D., M. Th. Matton-Van-Leuven, M.D., K. A. Eiring, M.S., R. Georgiade, M.A., and N. Georgiade, M.D. Duke University School of Medicine, Department of Surgery, Plastic Surgery Research Laboratory, and Division of Ophthalmology.

Twenty-four corneas of adult cats were used. Formalin-fixed sections were prepared representing the following groups: (a) fresh controls, (b) after soaking in the preservative fluid, 20-percent glycercol-80-percent balanced salt solution, (c) frozen at either —79°C. or —45°C. fixed during thawing, (d) frozen at same temperatures and fixed after complete thawing, (e) frozen, thawed and reconstituted in rabbit or horse serum. The sections were stained by hematoxylin-eosin and the following stains to demonstrate mucopolysaccharides: (1) periodic acid-Schiff, (2) alcian blue, (3) dialysed colloid iron and potassium ferrocyanide.

The fresh corneas and the ones soaked in the preservative fluid showed a regular pattern of distribution of the blue material (mucopolysaccharides) enveloping the stromal collagen fibers. When fixed during the thawing, the corneas frozen at —79°C. showed a slight irregularity in the distribution of the mucopolysaccharides, whereas the ones frozen at —45°C. were almost comparable

with the fresh controls. The corneas frozen at —70°C., fixed after complete thawing and during rehydration, showed marked dislocation of the mucopolysaccharides while the ones frozen at —45°C. showed only slight irregularities.

It was concluded that the thawing period was the most critical part in the whole process of preservation and that efforts should be directed toward the prevention of swelling with which the changes were associated.

**The influence of cycloplegia vs. mydriasis on the action of miotics: A preliminary report.** Robert A. Schimek, M.D., and Warren Lieberman, M.D. Department of Ophthalmology of the Ochsner Clinic and Ochsner Foundation Hospital and Tulane University School of Medicine, New Orleans, Louisiana.

Tonographic examinations were performed in a case of severe glaucoma (wide-angle) controlled by a strong miotic (Phospholine-Iodide). While under continuous influence of Phospholine-Iodide, mydriasis by Neosynephrine did not lower the coefficient of outflow but cycloplegia by Cyclogyl did reduce this value. The fact that mydriasis does not interfere with the tonographic outflow induced by miotics, but cycloplegia does interfere with this, may be a clue as to the site of action of miotics in controlling the intraocular pressure in glaucoma.

## Ophthalmic Miniature

As a physiological process of advancing years the scleral portion of this cribiform ligament tends later to become also sclerosed, so that the histological difference between the structure of the filtration network and the surrounding sclera is not so great, and in fact may be reduced only to a difference in the size of the fibres.

Primary glaucoma is produced by this sclerosis so narrowing down the meshes of the filtration network as to impede the aqueous outflow.

T. Henderson,

"The anatomy of the so-called pigamentum pectinatum irides and its bearing on the physiology and pathology of the eye."

Tr. Ophth. Soc. U. Kingdom, **28**:47, 1908.

# SOCIETY PROCEEDINGS

EDITED BY DONALD J. LYLE, M.D.

## COLLEGE OF PHYSICIANS OF PHILADELPHIA

SECTION ON OPHTHALMOLOGY

February 19, 1959

HAROLD G. SCHEIE, M.D., *Chairman*

### SURGICAL TREATMENT OF BLEPHAROPTOSIS

DR. RAYNOLD N. BERKE (by invitation): The final result of ptosis surgery depends on three factors: the skill of the surgeon, the nature of the ptosis, and the type of operation done.

However skilled the surgeon may be, it is still impossible to achieve a perfect cosmetic and functional result in all types of ptosis by any procedure available to us today. This is so for two reasons. First and most important is the complex nature of some types of ptosis, such as; ptosis complicated by severe blepharophimosis, ptosis associated with the jaw-winking phenomenon of Marcus Gunn, and ptosis due to complete third nerve paralysis. Second, is the observation that all ptosis operations carry some inherent disadvantages which of themselves prevent a perfect result.

*Frontalis ptosis operation.* If one is successful in fully correcting the ptosis in the primary position by suspending the lid from the brow, then after operation there is always lagophthalmos in looking down and ptosis in looking up unless the brow is elevated to raise the lid. For these reasons the frontalis type of operation is not the procedure of choice for all patients with ptosis, especially when the ptosis is monocular. However, when the ptosis is binocular and fully corrected in the primary position these objections are much less serious because the ptosis in upward gaze and the lagophthalmos in looking down are equal on the two sides.

It would seem, therefore, that the frontalis operation is the operation of choice for binocular ptosis when resection of the levator is contraindicated, and for monocular ptosis only when the levator and the superior rectus muscles are too weak to support the lid.

*Superior rectus ptosis operation.* The main advantages of suspending the lid from the superior rectus muscle are: the lid moves synchronously with the globe in upward and downward gaze; a good upper lid fold is produced; a natural curve of the upper lid margin results when wide adhesions are produced between the tarsus and the superior rectus muscle.

The disadvantages are: some hypotropia is usually present in upward gaze after operation even though the superior rectus is shortened at the time of operation; normal winking is destroyed and there is lagophthalmos in sleep with a tendency for exposure keratitis to develop.

For three reasons this type of operation should not be used for all types of ptosis. Despite these objections however, it is the operation of choice for jaw-winking ptosis when the superior rectus muscle is normal or near normal, provided the superior rectus is shortened to enhance its lifting power and a large part of the levator is excised to eliminate the jaw-winking phenomenon.

*Resection of the levator muscle.* Because resection of the levator is the only operation which can give a perfect result, most seasoned ophthalmologists believe that it is the operation of choice for all types of ptosis (except jaw-winking ptosis) when the levator action is adequate. However, there is an honest difference of opinion as to which operation—the internal or the external approach—gives the best results.

In order to resolve this question, I have analyzed the results of 186 operations done for congenital ptosis, 78 of which were done through the conjunctival approach and 108 through the skin route. Because the cases were all congenital and not selected in each group, and because the operations were all done at the same institution by essentially the same resident and attending surgeons, and

because all preoperative and postoperative examinations as well as the details of the operation were all collected and analyzed by the same person, this appraisal of the relative merits of the two procedures should be a fair and valid one.

This survey showed that the external approach produced one mm. more correction and about 20 percent fewer undercorrections than did the internal route.

When overcorrection followed the skin approach it was usually associated with good levator action (eight mm. or more) and a postoperative "lift" of the operated lid with respect to the cornea—that is to say the lid assumed a higher position on the cornea when healing was complete than at the end of the operation.

Undercorrection usually occurred when the levator action was poor (five mm. or less) and was associated with a postoperative "fall" of the lid, that is, the lid covered the cornea more when healing was complete than at the end of operation. When the levator action measured six to eight mm. in amount before operation the operated lid usually assumed the same position on the cornea as at the end of operation.

From this survey it would seem that:

1. The frontalis type of ptosis operation is the procedure of choice for complete bilateral ptosis with little or no levator action and for those cases of monocular ptosis where the levator and the superior rectus muscles are too weak to support the lid.

2. The superior rectus muscle should be utilized to correct the ptosis when associated with the jaw-winking phenomenon, provided the superior rectus is shortened to enhance its lifting power and a large part of the levator is excised to cure the jaw-winking.

3. Resection of the levator through the skin route is the operation of choice for congenital ptosis when some levator action is present, taking care to overcorrect the ptosis on the operating table when the levator action is poor and to undercorrect it when the levator is good.

William E. Krewson, 3rd,
*Clerk.*

## NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

446th meeting, January 21, 1959

HENRY L. BIRGE, M.D., *President*

### ANESTHESIA

DR. RALPH M. TOVELL (Hartford, Connecticut): I believe that satisfactory anesthesia can be achieved with two-percent procaine and I am still of the opinion that you can avoid the tachycardia and pallors that go with syncope on occasion with less than 1/50,000 adrenalin. Personally, I would be inclined to compromise and agree that, in small doses of procaine that are used retrobulbarly, there is no great hazard in using a total dose of four percent.

DR. ARTHUR C. UNSWORTH, (Hartford, Connecticut): It is only rarely that I use local anesthesia entirely. I think most of us in Hartford are using two-percent procaine with 1/100,000 adrenalin. There are always some areas of argument between the Department of Ophthalmology and the Department of Anesthesiology. The anesthesiologists usually prevail because they seem to have such good reasons for their arguments.

For some years I have insisted for my patients that intratracheal anesthesia not be used for any intraocular surgery. I have not allowed the nose or throat to be sprayed with topical anesthesia. The reason for this is that, postoperatively, some of my patients have sneezed and coughed, particularly the geriatric cases. And often there is a sinus drip. When the topical anesthesia begins to wear off their throat is full of mucus and they are apt to cough and expectorate and I think this raises their intraocular pressure temporarily.

Atropine or scopolamine I have liked in the older patients because it makes their mouths dry postoperatively but I think they are more apt to ask for and perhaps be given water or other fluids sooner than it is safe.

In my experience Dramamine has been of no help at all in preventing nausea. Sparine

I think is better and it controls restlessness much better.

DR. TOVELL: I have had a little more opportunity to cogitate about the problems of adrenalin. I think the saving grace in any concentration above 1/200,000 in ophthalmology is the fact that you use such small quantities. Now we in anesthesia often use much more solution when we are preparing for say a craniotomy. In such cases if we were to employ more than 1/200,000 we would surely get tachycardia and syncope.

DR. HENRY L. BIRGE (Harford, Connecticut): In the last few months I seem to be using a great deal less adrenalin. I would say that in nine out of 10 cases recently we haven't used it mostly because of hypertensive reactions. We have been getting along very well without it. I don't know why the ophthalmologist thinks adrenalin is required in so many cases. I think it is a hangover of one of our older ideas and we could and should re-estimate it.

DR. BRENDAN D. LEAHEY (Lowell, Massachusetts): It is obvious that more and more cataracts are being done under general anesthesia. Certainly it has gone that way in Hartford and I believe that in Cleveland and Detroit a great many of the men are using general anesthesia. We use very little of it around here. I only use it when these is a patient I think I can't control. Now the chief objection of those who don't use general anesthesia is that there is much more nausea after its use. One episode of the expulsive type of vomiting may dislocate some things inside the eye.

DR. TOVELL: We anesthesiologists feel that there is approximately 10 percent occurrence of nausea and vomiting following anesthesia. This varies in severity. If drugs and anesthetic agents, such as Cyclopropane or even sometimes ether, are used you will find the incidence higher than following the use of pentothal and nitrous oxide and muscle relaxants.

DR. BIRGE: It was quite a few years ago that we started to use general anesthesia and one of the reasons was that we believed the people who vomited were those who were most severely nervous. One of the advantages of present-day general anesthesia is that the patients don't get nervous. They are completely controlled and, therefore, I don't believe we see the vomiting and other results of stress that we used to see. I would say that less than 10 percent of my patients have any vomiting and usually that isn't of any importance at all.

DR. UNSWORTH: As to nausea, I think most children are apt to vomit after general anesthesia; certainly most of our muscle cases do. Our geriatric cases, intraocular cases particularly, rarely do whether they have general or local anesthesia. I think the most important step in avoiding vomiting in a patient is the preoperative preparation of the patient and the preoperative medication. If the patient comes down to the operating room completely relaxed and unafraid and doesn't care particularly what happens and is co-operative, then you will rarely have vomiting and other nervous phenomena. However, if the patient is not relaxed and is nervous and apprehensive, then the patient will be nauseated postoperatively.

MEMBER: Would some one say something about the amount of procaine to be injected? About a year ago I switched to Xylocaine and I am using a one-percent retrobulbar injection and also for the van Lint akinesia. It is a difficult thing to evaluate but I have the feeling that Xylocaine is far superior as far as my akinesia is concerned and also for blocking the extraocular muscles. There is not nearly so much motion of the globe. Does anyone else have anything to say about Xylocaine?

DR. TRYGVE GUNDERSEN (Boston): I think probably Xylocaine is fully as good as Novocaine. When we do our van Lint here we use about five cc. of procaine along the margin of the orbit. I particularly adhere to Gifford's technique of retrobulbar injection and use less procaine this way. I had two patients this morning and I don't think more than two cc. were injected in either case.

DR. TOVELL: I would like to comment on Xylocaine versus procaine. There are very few people who are truly sensitive to pro-

caine. In my 25 years in anesthesia I have not seem more than five such people. Many more are likely to be sensitive to Xylocaine.

### Disciform degeneration of the macula

Dr. Robert J. Herm (Waltham, Massachusetts), Albert O. Seeler (Cambridge, Massachusetts), and H. E. MacMahon (Cambridge, Massachusetts): The patient, now aged 42 years, was first seen by an ophthalmologist four years ago with a history of blurred vision. He was described as having "typical findings of central serous retinopathy." Vision was 20/20 in both eyes. General physical examination was negative.

Six months later he had a recurrence of blurred vision, O.S. He also showed a "yellowish dome-shaped reflex" in the center of the fovea. There was an elevation extending above this. His right eye was entirely normal.

Fourteen months later he had an episode of general malaise and a return of blurred vision, O.S. Vision was 20/15, O.U. In the left eye there was an area of edema and retinal elevation above the macula with some linear hemorrhages on the edges. There was a corresponding paramacular field defect inferiorly about 10 degrees in diameter.

The vision varied from day to day and when he was next seen, two months later, there was a yellowish elevated mass just above the macula with linear hemorrhage at its superior edge. It was obvious at this time that he had a typical disciform degeneration of the macula.

Six months later the mass had enlarged to occupy the entire macula area and was more elevated and there was more hemorrhage around and on the main lesion. Vision was 20/70, O.S. General physical examination was not remarkable. A skin-muscle biopsy of the right gastrocnemius was done. The report showed a combination of muscle necrosis and cutaneous vasculitis that was very suggestive of an underlying disease of allergic origin.

After three weeks of steroid therapy the patient's vision improved and there was a disappearance of some of the retinal hemorrhages. A skin and muscle biopsy of the same area as before showed an absence of the previously described lesions.

He was continued on steroid therapy, maintenance dose—70 mg. daily—for five months. His vision at the end of the fourth month was 20/70 O.S. There was a decrease in the elevation of the subretinal mass and an absorption of the retinal hemorrhages.

Two months later his vision, O.S., gradually decreased to 20/40-2, with a development of more retinal hemorrhages, perimacular edema, and early circinate retinopathy. Skin biopsy of the same general area was repeated and showed a picture of recurrent vasculitis.

The patient was returned to steroid therapy and in one week the perimacular edema was less and there was no fresh hemorrhages. Visual acuity improved to 20/30. However, the circinate retinopathy continued to increase. Later skin biopsy showed a minimal perivascular cellular infiltration.

Disciform degeneration of the macula, both senile and juvenile types, has been found co-existent with a wide variety of systemic diseases. These associations would appear to be fortuitous in most instances, although it is felt generally that atherosclerosis predisposes to the development of the senile type. This case is unique in that it demonstrates exacerbations and remissions of juvenile disciform degeneration coinciding with the exacerbations and remissions of a pathologically proven vascular disorder. The remissions were seemingly induced by systemic steroid therapy.

Charles Snyder,
*Recorder.*

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## LENS REGENERATION*

In mammals, regeneration of specialized tissue is exceptional and slight; but ophthalmologists are aware from daily observation that—rather surprisingly—some regeneration of lens fibers is not uncommon. Such regeneration raises a problem in extracapsular extraction of cataract, for the capsule left behind tends to get denser with time, and this denseness is not exclusively due to opacification of the capsule but results from some new lens fibers.

While oculists were very much concerned with this problem as long as some century and a half ago, experimental embryologists

* Reprinted from *The Lancet,* September 19, 1959, p. 396.

have become interested only quite recently. The determining role of the optic cup came to be appreciated from rather startling findings—for instance, that in the chick embryo the optic cup would build a lens out of any ectodermal tissue with which it was in contact: a lens could be made out of ectoderm that was destined to become abdominal skin if the optic vesicle was transplanted on to the abdomen. Later, regeneration of a missing lens became a tantalizing problem with the successful work on the amphibian eye by Stone and others. Now Russian workers have shown that regeneration of a high order is possible in the mammalian eye—so much so that one of these workers, P. S. Chanturishvili,[1] could speak hopefully last year at the Oxford Ophthalmological Congress of clinical possibilities. Apparently these lens fibers are derived from cells which are neural in origin, and which require for the initiation of fiber formation the products of cytolysis of epidermal elements.

Chanturishvili and his associates have shown that when small fragments of cytolyzing fetal tissues are introduced into the lens capsule of adult rabbits, from which all easily separable contents have been evacuated, regeneration will take place, giving something like a normal lens in contrast to the incomplete formation of lens fibers that are seen in untreated aphakic eyes.

The detailed experimental results reported at Oxford last year are now confirmed in a preliminary study by Stenhouse Stewart and 'Espinasse[2] of Hull. So far, experimental studies suggest that the regeneration of lens follows more readily on the evacuation of healthy lens matter from a mammalian eye than on the removal of cataractous lenses. Satisfactory regeneration of lenses in rabbits have, however, been obtained by Sikharulidze[3] after removal of chemically induced cataracts. Studies on these lines are now proceeding at Hull, where cataract is being produced by local irradiation.

In his experiments, Chanturishvili used conserved minced brain of mice as the necessary neural agent to initiate fiber production in the capsule of the extracted lens of rabbits. What other material can be used for this purpose is apparently still not decided. Despite the considerable theoretic and practical difficulties raised by this work, a substantial advance with clinical possibilities has clearly been made.

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## CORRESPONDENCE

### Odd corneal transplantation

Editor,
American Journal of Ophthalmology:

Not much has changed since I summarized, in the 1919 von Graefe's *Archiv fuer Ophthalmologie,* the disappointing results of grafting animal corneas to human eyes, and James H. Allen's six-year research project yielded the explanation that chemical differences between human and animal corneas are responsible for the failure of these attempts. However, in a report about his services as ophthalmologist under His majesty the Iman of Yemen, Dr. Sergej Sergejovich Golovin, a Russian-born, Prague-graduated son of the late Moscow professor of ophthalmology described, among other unusual experiences, satisfactory results of transplants from monkey corneas to man. (*La Presse Medicale,* **65**:193-194, 1957.)

Due to religious taboos of the Arabs, it was impossible to use human corneal material and so Dr. Golovin used material from the monkey Cynocephalus papio. One of these transplants remained clear for five years and seven months. Travel is difficult and patients rarely return to the clinic. One Yemenite, having lost one eye, obtained fair vision from the other eye after such an op-

eration but, returning to his native village, was exposed to ostracism from his neighbors who considered him unclean because of his carrying a part of a monkey in his body. He was prevented from participating in religious services and therefore returned to the Taiz hospital requesting the removal of the "unclean" part from his only seeing eye. The hospital staff by lengthy and very elaborate examination persuaded the patient that the monkey tissue was gone and that his eye was completely human again. The statement that he was clean now and could participate in the services in the Mosque did not convince the patient too much. As a consequence, Dr. Golovin could not continue the use of monkey corneas for transplantation.

(Signed) K. W. Ascher,
Cincinnati, Ohio.

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### Label with name of drug

Editor,
American Journal of Ophthalmology:

The addition of the above five words to every prescription will benefit both you and the patient. Mystery as to the nature of medications is an unwarranted and obsolete tradition. The following advantages accrue from labeled prescriptions:

1. If the patient is taking more than one medication, a change in instructions concerning one is less likely to result in confusion. (Which bottles do I stop using, Doc?)

2. When one of multiple prescriptions is exhausted, it can be identified for refilling. (Doc, the round bottle is empty.)

3. Several doctors caring for the same patient can more easily co-ordinate treatment. (Why are you giving me Diamox for my eyes when the heart doctor uses it for my edema?)

4. A consultant or new physician need not change or discard perfectly adequate, but unknown, medications. This is a very common unnecessary expense to patients.

5. In case of emergency, the nature of the patient's medications can more rapidly be determined.

6. Medications to which there is a known allergy are less likely to be given without the patient's recognition.

7. Re-use of remaining medication later in the course of the disease or by another member of the family becomes possible upon your advice.

8. Economy, in these days of high drug costs, is achieved for the various reasons already given.

9. Dispensing errors may more readily be detected. (And they happen!)

A great deal of confusion could be avoided if prescriptions were clearly identified. Certainly in matters as important as human health, there is no room for uncertainty.

(Signed) William H. Havener,
Columbus, Ohio.

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### An unusual cataract extraction

Editor,
American Journal of Ophthalmology:

I am sending a note on a curious operation I performed recently and hope you will find it interesting enough to publish.

F.A., a 28-year-old man, was first seen November 10, 1959, complaining of blurred vision of the right eye. Three days earlier, while hammering a piece of steel, he had felt something hit his right eye, causing some pain. Since the pain had subsided after a few minutes, he went on with his work. Next day he had some blurr in the right eye and, as this was getting worse, he came for advice.

Examination showed a painless white right eye but a whitish lens could be seen. Tension was normal, as were light reflexes. With the slitlamp, a very small penetrating corneal wound could be detected, about half way between the center of the pupil and the 4-o'clock position. There was a small puncture on the anterior lens capsule, in the same diameter but closer to the center of the

pupil. The lens was partially opacified (traumatic cataract) and inbedded in it was a small foreign body, slightly rusty, and with the shape of a small thorn, about 3.0 mm. in length and about 0.75 mm. in diameter. It was oriented on the line of the corneal and anterior capsule wounds, did not reach the posterior capsule, and was completely inside the lens. It looked magnetic but I did not make a test with the giant magnet for fear of dislocating the lens.

A week later the cataract was completely formed and vision was reduced to light perception.

At operation on November 20, the following technique was used:

Mydriasis was obtained with one-percent atropine drops, O'Brien's nerve-block with two-percent Xylocaine, four-percent drops of Novesin were repeatedly instilled, and a retrobulbar injection of 1.5 cc. of two-percent Xylocaine was made. A 3-0 silk suture was passed medially on the upper eyelid, about three mm. from its margin, a 3-0 silk bridle suture was passed under the superior rectus belly, and a preplaced 6-0 silk Ethicon corneal-episcleral suture (Liegard) was placed.

A limbal incision was made with a von Graefe's knife, with puncture and counterpuncture at the 9- and 3-o'clock positions the blade coming out between the intracorneal and intra-episcleral ends of the Liegard suture.

A small peripheral iridectomy was done at the 12-o'clock position with Hess's forceps and deWecker's scissors.

A solution of 1:5,000 alpha chymotrypsin (Quimotrase, of the P.E.V.Y.A. Laboratories of Barcelona, Spain) was then injected into the anterior chamber and into the posterior chamber by way of the iridectomy opening.

After waiting for about three minutes, the lens became slightly globular and its anterior surface was seen to raise. I then raised the corneal flap, pulling it by the corneal side of the Liegard's suture and applied the tip of an Alnico 5 permanent hand magnet (manufactured by General Electric) to the anterior surface of the lens. With the foreign body inside it the lens promptly adhered to the magnet, and was completely removed without the smallest difficulty.

The chamber was then flushed with warm normal saline solution, to wash out the Quimotrose. The Liegard suture was tied, two more 6-0 Ethicon sutures (corneoscleral) were passed at the 10:30- and 1:30-o'clock positions, an air bubble was injected into the anterior chamber, and a binocular dressing applied. Recovery was uneventful, and the patient was dismissed from the hospital a fortnight later.

On December 7th, vision of the right eye, with +12D. sph. $\bigcirc$ +1.0D. cyl. ax. 180°, was 6/6.

Of course the lens could have been removed without the magnet but I thought it safer to do it in the way described for the capsule looked quite tense and might tear if a capsule forceps was applied. The lens could also have been removed by suction but I don't like the method (I think all erisophakes a little clumsy, though I have achieved quite good results with their use), or once zonulolysis was achieved, by pressure and counterpressure (Smith's technique). Anyway with the Alnico 5 magnet, it was an easy and safe operation.

Though I am not sure of the advantages of alpha chymotrypsin in senile cataract surgery (I only use it when I find any difficulty in grasping the capsule with the forceps or when I find a very tough zonule), I believe its use in cataract extraction in young persons is definitely useful. I have used it in three traumatic cataracts in men aged 25, 28, and 35 years (a very small series, I know) and each time zonulolysis was perfect and the lens was removed in toto without difficulty.

A curious thing happened in all three of these cases. After the delivery of the lens, the iris looked as if it was being pushed forward. There was no tendency of the wound

to gape, nor of the iris to bulge into it and get incarcerated. Instead, the iris looked cone-shaped, as if it was being pushed from behind by a swollen vitreous. Is this an effect of alpha chymotrypsin on the vitreous? I don't know, and I don't know either if this fact has been observed by others. I believe it is worthy of attention for alpha chymotrypsin may have deeper effects than is generally believed.

(Signed) E. Corrêa de Barros,
Avenida dos Aliados, 184
Oporto, Portugal.

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## Chemical burns treated with egg membrane

Editor,
American Journal of Ophthalmology:

In the September, 1959, issue of The American Journal of Ophthalmology, Antonin Heinc, M.D., Czechoslovakia, has written an article entitled "Chemical burns of the eyes treated with egg membrane." Dr. Heinc states that we (Crolls) advocated the closed treatment of caustic chemical burns of the eye. This is *not* a fact. Indeed, we wonder if the author read our original article which was published in the November, 1952, American Journal of Ophthalmology, Vol. 35, No. 11. It is axiomatic that any burn of the eye, acid or alkaline, should be thoroughly irrigated. In our original paper we strongly advocate what every ophthalmologist knows—thorough and prolonged irrigation of the chemically burned eye.

Dr. Heinc writes at great length about his experiments with rabbits, in which he caused lime burns and then treated these burns with the insertion of egg membrane to prevent corneal opacities. His results were inconclusive and he concludes that the egg-membrane form of therapy is not helpful in lime burns. Rabbits, it must be recogized, are poor subjects for corneal experiments of this type, for rabbits readily become infected, and the cornea becomes opaque. After reading this method of causing lime burns in the conjunctiva, it strikes us that Dr. Heinc, at the same time, also caused deep lime burns of the cornea. Of course, deep lime burns of the cornea will cause corneal opacities regardless of the treatment. After he caused lime burns of the conjunctiva in the rabbits, Dr. Heinc did not irrigate the injured eye. Yet early irrigation of the eye is the most essential part of the treatment and regardless of the type of burn, the eye should be immediately and copiously irrigated with normal saline solution or, if that is not available, with tap water. With an intravenous saline bottle attached on a stand, the nozzle of the tubing may be used to direct the stream of water into all portions of the eye. Particular attention should be given to the fornices and every effort should be made to remove the solid particles hidden beneath folds of conjunctiva.

In terms of procedure, the eye is first well irrigated and all debris is meticulously removed. Vision is taken, pontocaine (0.5 percent) and fluorescein are used, and with the aid of a slitlamp, the amount of damage is estimated. In minor eye burns, irrigation and antibiotic eye salves are sufficient to prevent permanent corneal damage. However, where there is deep corneal staining and apparent damage to deeper corneal and conjunctival tissues, something should be done to separate the injured conjunctiva from the cornea; this must be done in order to stop the constant irritation of cornea by the injured conjunctiva and thus prevent corneal opacities, vascularization, symblepharon. In our experience the egg membrane, an inert tissue, serves the purpose very well.

In 1952, we reported on 26 severe lime burns of the eyes. Since 1952 we have had 24 severely injured eyes from alkaline burns. All have been treated with copious irrigation, insertion of egg membrane, antibiotics, and, on removal of egg membrane, steroid eyedrops and salve; if edema of the

cornea persisted, corticosteroids by mouth were also used. We obtained excellent results—no corneal damage in 18 cases, superficial corneal opacities in six cases, and vascularization of the cornea with symblepharon formation in two cases, cases that received late egg membrane therapy.

Dr. Heinc states the application of egg membrane over cornea interferes with lacrimation and is traumatic. Our method of treating lime burns of the eye with irrigation and insertion of egg membrane does not interfere with lacrimation. Tearing continues and dilutes the residual chemical, and egg membranes does not stop the normal process of tearing. Applying the egg membrane over the cornea and suturing superiorly and inferiorly only the superficial conjunctival tissue and the egg membrane, in order to prevent the egg membrane from sliding is definitely not traumatic.

Dr. Heinc reports one case of severe lime burn with poor result, after using egg membrane over the cornea; yet this case was treated late. Surely one case does not prove that insertion of egg membrane in severe lime burns is not effective. Where the lime burn is severe both to the conjunctiva and cornea, no treatment is known that will prevent permanent corneal opacities. However, the egg-membrane method is an adjunct form of therapy and will aid in treatment of many lime burns.

A. L. Brown in 1941 states that constant contact of the cornea with the inflamed, burned conjunctiva causes irritation of the cornea and, as it is not the accumulated caustic which produces corneal damage, Dr. Brown recommended separation of the opposing injured conjunctival and corneal surfaces by inserting rabbit peritoneum. We agree with A. L. Brown and we have done the same thing, only we have substituted egg membrane, instead of rabbit peritoneum, to separate the injured conjunctiva from the cornea in order to keep the cornea clear and prevent corneal opacities. In this way, the egg membrane is an excellent form of therapy in severe alkaline burns.

(Signed) Leo J. Croll,
Maurice Croll,
Detroit, Michigan.

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## Suture spreader improved

Editor,
American Journal of Ophthalmology:

The simple suture spreader devised by R. N. Lehman and M. F. McCaslen from two-inch safety pins (The Journal, **48**: 676-677 [Nov.] 1959) is helpful with preplaced corneoscleral sutures of any material. After the surgeon has placed the loop over the hooks, if the thread belonging to each side of the loop is placed over the corresponding hook and then passed through the ring of the spring, entanglement of the sutures is avoided and the operator knows immediately which side of the loop belongs to which thread.

The suture spreader can be improved by utilizing, instead of safety pins, the Hesseltine umbilical cord clamps. These have the appearance of safety pins and the desired length, being 2⅜ inches long. They are superior to common safety pins in being made of stainless steel and in having a larger and more delicate spring. They are readily obtainable from any surgical supply house and are quite inexpensive; a set of three costs but 50 cents. All "rustproof" safety pins are now made of brass and nickle-plated. During World War II, when brass was in short supply, stainless steel safety pins were substituted but are no longer available.

The Ethicon Company has recently produced 6-0 green Mersilene polyester fiber, double-armed with micropoint needles. Consequently, further to minimize confusion when multiple preplaced sutures are used, black and green thread may be alternated with advantage.

James E. Lebensohn.

# BOOK REVIEWS

ROENTGENOLOGIC DIAGNOSIS IN OPHTHALMOLOGY. By Edward Hartmann, M.D., and Evelyn Gilles, M.D. Philadelphia, J. B. Lippincott Company, 1959. 348 pages, 497 illustrations, bibliography (since 1937), index. Price: $15.00.

In 1936, Edward Hartmann, who is widely known and admired in the United States, chief of the Ophthalmic Department, Lari Boisière Hospital and American Hospital in Paris, brought out a superb clinical atlas, *La Radiographie en Ophtalmologie*, published by Masson et Cie, Paris, under the auspices and co-operation of the Société Française d' Ophtalmologie. It was a well-planned and executed book, soon out of print. In 1955, Hartmann and Evelyn Gilles, who is chief of the Roentgenology Department, Quinze-Vingt Ophthalmic Hospital and associate in roentgenology, St. Antoine Hospital and American Hospital in Paris, produced their excellent book, *Radiodiagnostic en Ophtalmologie*, published by Masson et Cie, Paris. In THE JOURNAL (**43**:482, 1957), I reviewed their book with enthusiasm. It is therefore, with great pleasure that I can draw your attention to it once more in an English translation by G. Z. Carter, M.D., assistant professor of ophthalmology, Albert Einstein College of Medicine, who has done a superb job of it. The work is edited by Conrad Berens, M.D., whom we all know so well and admire. Hartmann is a master of English and Carter and Berens obviously know their French. The result is a lucid and flowing account of the subject which, so far as I know, is not available in book form written expressly for the ophthalmologist. The illustrations are sharp and clear, the paper of the highest quality and the printing is excellent. It is a book to own, to study, to refer to, and to cherish. We are most grateful to all those who had a part in bringing to us the edition in English of a work that is justly popular, classical and standard.

Derrick Vail.

INVESTIGATIONS CONCERNING THE METABOLISM OF THE CRYSTALLINE LENS. By Prof. Mark v. Stackelberg, Ph.D. Cologne and Opladen, Westdeutscher Verlag, 1959. 39 pages, 10 illustrations. Price: DM 11.50.

This monograph appeared as No. 710 in the series Research Reports of the State of Nordrhein-Westphalia, published by the Ministry of Education. It concerns itself with the oxygen metabolism of the lens, the effect of X-rays on its metabolism, polarographic examinations of the aqueous of man and rabbits, and investigations of glycolysis and the nucleotide metabolism.

The methods used in these investigations are merely enumerated. No technical details are stated. The purpose of the publication is only to give an account of the results obtained. A wealth of information is to be found in these pages by the research worker interested in this particular field. However, certain facts are of some consequence to the practising ophthalmologist.

The oxygen consumption of the lens is a very sensitive indicator for its normal and impaired metabolism. It is determined by the polarographic method. The absorption of oxygen depends on the age of the lenses and the partial pressure of oxygen. Pilocarpine in a concentration of $10^{-3}$ M seems to interfere with the oxygen metabolism of the lens. Therapeutic concentrations are as high as $10^{-1}$ M!

X-ray irradiation of the culture medium causes hypoxia which, in addition to other possible damage, must be considered in evaluating the total impairment caused by actinic insults.

It could be proven that the available oxygen alone is not sufficient for the requirements of the lens. Part of it is supplied by dehydroascorbic acid. This mechanism seems to be governed by acetylcholine.

The investigations of glycolysis and the nucleotide metabolism were carried out with the aid of radioactive isotopes. $P^{32}$ in the from of orthophosphate was added to the culture medium. The results thus obtained

explained quite logically the gradual reduction in growth of the aging lens.

Stefan Van Wien.

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BLINDNESS IN WEST AFRICA. By F. C. Rodger, M.D., Ch.M., D.O.M.S. With a foreward by Sir Stewart Duke-Elder. London, H. K. Lewis & Co., Ltd., 1959 (published for the Royal Commonwealth Society for the Blind). 221 pages, 96 illustrations, colored frontispiece, 6 maps, references, appendices, index. Price: £3, 10s.

This is a fascinating and well-written book by Dr. Rodger who led a team, the second of its kind, into Northern Ghana, the Cameroons, and Nigeria to survey the incidence and cause of blindness in these territories in 1952-1956. The team traveled more than 10,000 miles in a convoy consisting, among other vehicles, of a mobile operating theatre and clinic and carried three tons of special equipment. We are told "that more than half of the villages visited were deep in the bush, sometimes having to be approached by river, on foot or on horseback. At times a way was forced through woods, along primitive tracks, or through deeply swollen rivers, or miles of soft sand." (*The Times Weekly Review*, Nov. 12, 1959).

The main causes of blindness were found to be cataract, trachoma, onchocerciasis, leprosy, smallpox, measles, conjunctivitis, malnutrition, and the use of local (witch) remedies. The author was particularly impressed and intrigued with onchocerciasis and its endemic role in leading to blindness in all areas visited. Dr. Rodger has helped to solve some of the confusion surrounding the nature of the choroidal lesions found in frequent association with onchocerciasis, by reporting histopathologic studies which revealed (a) an inflammatory lesion and (b) a circumscribed degenerative lesion due to the organism. The anterior lesions of the cornea and anterior segment are obvious and well known, and Dr. Rodger found them quite common in the areas he visited. He showed that there are some 200,000 blind among the 12 million inhabitants in the areas surveyed. In Europe the blindness rate is about 200 per 100,000, whereas in areas where onchocerciasis was rife, it rose steeply to 1,500 per 100,000; in Ghana this figure was doubled.

The illustrations and printing are excellent, and while the author says little about his daily adventures, it is easy to read between the lines and get the same excitement you experienced as a boy when you read Stanley's *In Darkest Africa*.

The problems presented are massive and heart breaking. Treatment is difficult to give and the results are often not apparent at the time. The spaces are huge, the ignorant and superstitious people are primitive; the teeming population lives in filth and poverty. And yet this book inspires hope and enthusiasm and confidence that, as the African states emerge, as they are now doing, these problems will be solved. Dr. Rodger's fine book, of interest not only to the scientist and physician, but also to the compassionate layman, will play a pioneer role of great significance in the ultimate conquest of the diseases that cause blindness in the Dark Continent. There is so much to do.

Derrick Vail.

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THE PREPARATION OF MEDICAL LITERATURE. By Louise Montgomery Cross, M.A. Philadelphia, J. B. Lippincott Company, 1959. 441 pages, including two appendices, 80 illustrations, index. Price: $10.00.

Miss Cross is famous, and as you read and study her book you will easily see why, in the New York City area for her superb work as a manuscript editor and professional medical writer of some 25 years' experience.

Section one is titled "Planning the paper or book." Then follow sections on gathering material for a paper or book, writing the journal paper or book, style, styling, illus-

trations, and editing. Each section contains pertinent subsections (40 in all) and each is a gem of logic, clarity, and example. Shirley Baty, medical illustrator, the Memorial Center for Cancer and Allied Diseases, contributes a fine chapter on charts and graphs. In addition the author says "Miss Daisy Stilwell, free lance medical illustrator (with Miss Baty) have read the entire section on illustrations and have made comments such as could be made only by the practising artist."

A number of books dealing with this subject have appeared recently but, in my opinion, this is by far the best of the lot. Every would-be medical author (and who isn't) must get a copy and learn its contents thoroughly. All editors owe a great debt to Miss Cross for her painstaking and illuminating work and, if it is as widely read as it should be, the burden of our work will be gratefully lightened.

Derrick Vail.

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PRE-SCHOOL VISION. By Richard J. Apell, O.D., and Ray W. Lowry, O.D. New Haven, Connecticut, Gesell Institute of Child Development, 1959. 189 pages. Price: $7.50.

This timely monograph focalizes the importance of visual evaluation in the preschool child. Though no new tests or methods are introduced, the consideration of vision within the framework of the developing child is stressed and amply clarified. The visual examination should preferably be given in the morning when the child is not fatigued. A children's corner in the reception room, where youngsters play, will facilitate their adjustment. Casual comments about wearing apparel or the day's activity help to overcome shyness. Most children co-operate better when the parent is not in the same room. Though a two-year-old does not accept a lens before one eye easily, he may adapt better to lenses before both eyes. At the four-year level the acuity with the E test reaches 20/25 to 20/20 and the average score with the Wirt stereotest is 50 to 60 percent. The achieving child is a good listener, appreciates humor, and shows a high interest in eye-hand activity. The nonachieving child has marginal interests and avoids eye-hand activities. "Whereas, the examination is a challenge to the achiever, the nonachiever is a challenge to the examiner." Assuming that the child is not strabismic nor suspect of a high refractive error, the first routine visual examination is best done at the age of four years.

This book, written by optometrists for optometrists, is not lacking in optometric mist. Nevertheless, to quote from the foreword by Arnold Gesell, M.D., it does give "a better understanding of vision in terms of the child; a better understanding of the child in terms of his vision."

James E. Lebensohn.

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VOCATIONAL REHABILITATION COUNSELING OF BLIND PERSONS: A CAREER WITH A CHALLENGE. By Maxine Wood. Illustrations by Corinn Rowe. New York, American Foundation for the Blind, 1959. 23 pages, paperbound. Price: Gratis.

As early as practicable the newly blinded should stop mourning for their dead eyes and contact the state agency for the blind which will supply information on the community services and provide the guidance of a rehabilitation counselor. Under U.S. Public Law 565 any blind person of working age is eligible for free rehabilitation services, including counseling, training and help in finding a job. If special lenses can be of help, they will be provided also. The counselor fits his vocational program to the individual after careful appraisal of his assets and liabilities. The rehabilitated blind can earn a living, raise families and enjoy their favorite hobbies. Many blind youths have been graduated from college and are working in the professions of law, teaching, journalism, advertising, insurance and nursing.

James E. Lebensohn.

# ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

## CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

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## 1

## ANATOMY, EMBRYOLOGY, AND COMPARATIVE OPHTHALMOLOGY

Szeghy, G. **Examination of interfibrillar spaces in the intact and damaged cornea.** Szemeszet **96**:152-155, 1959.

By means of the injection method described in the literature, communications could be demonstrated between several fiber layers. In leucoma corneae the interfibrillar spaces are narrow and irregular in comparison with the normal. Paraffin injected near the deep corneal vessel includes several fiber layers and shows irregular patterns. These conditions cannot be observed with the superficial vessel. After the dissolution of the sticky substance, paraffin strips are broader than in the intact tissue. In living rabbits the intracorneal injection of paraffin leads to a change of the vessel pattern, vessels passing along the paraffin strips. One of the prerequisites of corneal vascularization is the change in the consistency of corneal tissue due to physical or chemical factors. Gyula Lugossy.

## 2

## GENERAL PATHOLOGY, BACTERIOLOGY, IMMUNOLOGY

Diekhues, B., Conrads, H. and Wagner, K. **Serologic examinations in rheumatic diseases of the eye.** Klin. Monatsbl. f. Augenh. **135**:516-520, 1959.

Antistreptolysin titer was compared with the Waaler-Rose and the latex test in 82 cases of rheumatic ocular disorders. The principle of the Waaler-Rose test consists of agglutination of sensitized erythrocytes. In the latex test colloidal rubber particles are agglutinated by the serum of patients with primary chronic polyarthritis. The antistreptolysin titer was positive in 21 cases, the latex test in three, the Waaler-Rose test in only two of the cases. Negative serologic examination in the majority of the cases is explained by the absence of a specific "rheuma factor" which is present in polyarthritis but absent in rheumatic uveitis. (1 table, 23 references)

Gunter K. von Noorden.

Mitsui, Y., Hanna, L., Minoda, R., Ogata, S., Kurihara, H., Okamura, R. and Miura, M. **Experiment on human volunteers with adenovirus type 8.** Brit. J. Ophth. **43**:540-547, Sept., 1959.

It is well established that adenovirus type 8 is the causative agent of epidemic keratoconjunctivitis since it has been isolated from patients all over the world.

This study was undertaken to determine what immunity to the disease results from vaccination with the agent. Two strains were used and made into a suitable vaccine which was known to produce no ill effects. A series of volunteers was vaccinated at weekly intervals and subsequently inoculated with fresh cultures after four to nine weeks. They were then carefully observed during the two weeks following the inoculation. Control volunteers who had not been vaccinated promptly developed the typical picture of the disease while those who had been vaccinated presented no clinically observable effects. These vaccinees were shown to have developed specific neutralizing antibodies to the virus and the immunity was strictly type-specific. (15 references) Morris Kaplan.

## 3

### VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Balik, J. **Urea secretion into the lacrimal fluid in keratoconjunctivitis sicca.** Klin. Monatsbl. f. Augenh. **135**:533-537, 1959.

Urea level of tears and blood was determined in 33 patients with keratoconjunctivitis sicca and in an equally large group of healthy subjects. The results were compared and evaluated statistically. A constant relation between tear and blood urea levels could not be established in the two groups. The ratio of tear urea and blood urea levels, however, was higher in the group with the disease. These findings support the belief that irregular lacrimal excretion is present in patients with keratoconjunctivitis sicca. (1 figure, 2 tables, 1 reference) Gunter K. von Noorden.

Boros, B. and Takats, T. **The action of hydergine on the isolated iris muscle.** Klin. Monatsbl. f. Augenh. **135**:538-545, 1959.

The adreno-sympatheticolytic action of the drug could not be demonstrated for the isolated cat iris. Likewise, no alteration of the parasympathetic tonus was observed under the influence of hydergine. Hydergine remains ineffective in ocular diseases which are characterized by sensitization of the vasoconstrictors. The drug does not seem to exert a significant effect on the regulation of the vegetative tonus of the ocular vascular structures. (4 figures, 15 references) Gunter K. von Noorden.

Bürger, M. **The aging of the eye.** Klin. Monatsbl. f. Augenh. **135**:609-632, 1959.

Aging, in the author's experience, begins with conception and ends with death. The term "biomorphosis" characterizes the constant alterations which the organism undergoes during the entire life. This term should be substituted for "gerontology" which applies only to aging processes in senescence. The study of aging processes has to be limited to bradytrophic tissues, tissues with low metabolic rate and low oxygen consumption. The cornea and the lens are bradytropic tissues in the eye. Such structures suffer a common fate during aging inasmuch as dehydration occurs in all bradytropic tissues. This results in increased tissue density and increased protein content. Increased tissue density, on the other hand, causes decreased elimination of catabolic substances, such as calcium and cholesterin which are stored in the tissue. Chemical changes during aging were studied in corneas and lenses of cattle. Progressive dehydration with age, as well as an increase in nitrogen content, were found to be present and compared to similar changes in human skin and cartilage. Similar chemical aging processes are responsible for the development of senile arcus, cataract, loss of accommodation, vitreous changes, decreased corneal sensitivity, and pupillary diameter. The functional correlation between bradytropic tissues was demonstrated by a

comparison between the velocity of the pulse wave and the range of accommodation during the course of life. It was concluded from this study that the nature of the aging processes taking place in lens and blood vessel walls is identical. (16 figures, 7 tables, 18 references)

Gunter K. von Noorden.

Conrads, H. **The influence of chloroquine on uveitis in animal experiments.** Klin. Monatsbl. f. Augenh. **135**:654-658, 1959.

A suspension of killed tubercle bacilli was injected into the eye in two groups of rabbits. One group had been treated for 80 days with 10 mg. chloroquine daily prior to the experiment and received the same dosage thereafter. In this group the injection resulted only in cell migration and exudation into the vitreous. In the untreated group the injection was followed by an extensive disseminated chorioretinitis. Combined therapy with cortisone and chloroquine is therefore recommended in treatment of endogenous uveitis. (5 figures, 20 references)

Gunter K. von Noorden.

Graymore, C. and Tansley, K. **Iodoacetate poisoning of the rat retina. II. Glycolysis in the poisoned retina.** Brit. J. Ophth. **43**:486-493, Aug., 1959.

Iodoacetate inhibits the glycolytic enzyme phosphoglyceraldehyde dehydrogenase. A sublethal retinal dose of iodoacetate plus malate inhibits up to 66 percent of glycolysis within ten minutes and the glycolysis returns to normal after three weeks. The highest tolerated dose results in a 75 percent inhibition after 10 minutes. The glycolytic rate, after recovery, remains at 50 percent. The glycolytic activity of the visual cells is higher than that of the rest of the retina. (3 figures, 1 table, 18 references)

Irwin E. Gaynon.

Newhouse, J. P. and Lucas, D. R. **Effects of parenteral iodoacetate and other thiol reagents on the rabbit retina.** Brit. J. Ophth. **43**:528-539, Sept., 1959.

In 1951 it was shown that a single intravenous injection of 15 to 30 mg. of neutralized iodoacetic acid per kilogram of body weight would do considerable damage to the rabbit retina and it was felt that this was due to a fall in glycolysis of the retina. Other thiol agents did not produce this effect. In this study this work was repeated in order to note the sequence of events of this damage. The retinas were examined biochemically and histologically at various times from 5 minutes to 24 hours after the intravenous injection.

A depression of both respiration and glycolysis was noted within five minutes and damage to respiration endured more than 24 hours. There was nuclear pyknosis within four hours which continued to increase in severity so that few nuclei remained intact after 24 hours and the rods themselves had become necrotic. This occurred in the visual cell layer as well as in the inner layers.

Four other thiol agents which are more toxic to the retina in vitro were found to produce no untoward effects. The authors suggest that the sodium iodoacetate used did not act entirely locally within the retina but there must be other extrinsic factors. (4 figures, 25 references)

Morris Kaplan.

Pedler, C. **Studies on developing retinal vessels.** Brit. J. Ophth. **43**:558-564, Sept., 1959.

It has long been firmly established that increasing the oxygen supply to the immature retina results in closing of the vessels but the actual mechanism has not yet been finally determined. Some experiments have led to the hypothesis that this obliteration of the vessels might well be caused by mechanical pressure resulting

from swelling of the surrounding retinal tissue. Such swelling is seen after the intake of solutions containing sodium fluoride. This paper reports the results of experiments investigating this possibility.

One of each of many pairs of animal eyes was injected intravitreally with a solution of sodium fluoride and the eyes examined histologically after varying periods of time. The variations in thickness of the retinas as well as any change in the wet weight-dry weight ratio were carefully noted. These were also compared to results after injection with normal saline solution. The results indicated that under certain conditions the injection of the fluoride solution did produce retinal swelling in the immature retina but not in the adult tissue and that the inner retinal layers, particularly the inner plexiform layer, are largely responsible for the change. Since the vessel walls in the immature retina are actually only a delicate endothelial tube lining a space, it could be concluded that edema of the retina could obliterate the vessels effectively. (8 references) Morris Kaplan.

Radnót, M. and Pajor, R. **The action of alpha-chymotrypsin on the cornea.** Klin. Monatsbl. f. Augenh. **135**:633-637, 1959.

Increased incidence of transient corneal opacities near the incision were observed in 14 cases of surgical zonulolysis. This observation led the authors to study the action of the enzyme on rabbit corneas. Intralamellar injection of the enzyme resulted in severe corneal necrosis. The histologic sections are demonstrated. (5 figures, 7 references)

Gunter K. von Noorden.

Schmidt, J. **The isolation of neuraminic acid from eye tissues.** Ophthalmologica **138**:314-316, Oct., 1959.

Neuraminic acid (NAA) is a characteristic component of a lipopolysaccharide isolated from gray (brain) matter by Klenck in 1941. In diseases such as amaurotic idiocy (Tay-Sachs) and lipochondrodystrophy (Pfaundler-Hurler) the NAA content of gray matter is significantly altered. The author describes the isolation of NAA from various portions of cattle eyes—Descemet's membrane plus endothelium, aqueous, vitreous and retina. (21 references) Peter C. Kronfeld.

Silva Pinto, M., Castro Correia, J. and Coimbra, A. **Retinal changes caused by experimental chorioretinal circulatory insufficiencies.** Ophthalmologica **138**:274-286, Oct., 1959.

One or more posterior ciliary arteries were obliterated in rabbits by cauterization at their place of entry into the sclera. The effects of this procedure upon choroid and retina were studied by morphologic methods. The effects were severe and clearly indicated that in the rabbit the posterior ciliary arteries are end arteries and that the choriocapillaris does not provide functional anastomoses between areas fed by different arteries. (4 figures, 16 references) Peter C. Kronfeld.

Tupinamba, J. **Enzymatic zonulolysis.** Arq. brasil de oftal. **22**:51-53, 1959.

The author summarizes his experiences with alpha-chymotrypsin in 14 cataract extractions in patients whose ages ranged from 35 to more than 61 years. A dilution of 1 to 5,000 was used according to the technique of Barraquer. The enzyme is recommended for cataracts in the young, complicated cataracts, and in myopia since it eliminates traction on the ciliary body with the danger of detachment of the retina. It also reduces the number of extracapsular extractions, retraction of the capsule, secondary membrane formation, and the postoperative iridocyclitis which follows mechanical rupture of the zonule. James W. Brennan.

## 4

## PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Ayberk, Nejat. **The treatment of amblyopia.** Istanbul Göz Klinigi Bull. **5**(17): 137-145, Oct., 1959.

The author describes his methods of orthoptic exercises and calls attention to the dangers in the use of atropine and occlusion. (7 figures, 26 references)

F. H. Haessler.

Brockbank, G. and Downey, R. **Measurement of eccentric fixation by the Bjerrum screen.** Brit. J. Ophth. **43**:461-470, Aug., 1959.

Occlusion of the better eye produces no improvement in an amblyopic eye with eccentric fixation. Eccentric fixation is relatively common. For evaluation a two-meter Bjerrum screen is used. The distances and angles between the center of the macula, the eccentric fixation point, and the center of the blind spot are measured with a rotary tangent rule. The normal eye is examined first, the blind spot is plotted, and the angle between the macula and the center of the blind spot is measured. The normal eye is then covered. The test is repeated on the eccentric fixing eye. The scotoma is also plotted. (6 figures, 1 reference)

Irwin E. Gaynon.

Konstas, K. **Excessive accommodation.** Ophthalmologica **138**:292-301, Oct., 1959.

The condition described by the author as excess of accommodation corresponds closely to the functional accommodative spasm of Duke-Elder and to the tonic spasm of accommodation with pseudomyopia, as the condition is usually called in the U.S.A. The condition occurs in children and young adults and is characterized by tonic accommodative efforts markedly in excess of the amount necessary for the task at hand. This excessive accommodative effort leads either to asthenopic difficulties during close work or to a variable degree of blurring of distance vision. Dynamic retinoscopy in the darkroom with points of fixation at various distances usually discloses the excessive accommodation or pseudomyopia. Under atropine the true basic refractive state proves to be hyperopia of small or moderate degree. The disturbance is usually of psychosomatic origin and responds somewhat to psychotherapy. (7 references)

Peter C. Kronfeld.

Lombard, G. **Visual acuity in low illumination.** Arch. d'opht. **19**:634-656, Sept., 1959.

This is the first part of an exhaustive review of the subject of vision under conditions of low illumination. The review must be read in its entirety to be appreciated. Subject headings in this first portion include the definition of visual acuity and a discussion of the factors affecting the determination of visual acuity, such as the technique of testing, the role of distance, and the effect of minor movements during the fixation period, the so-called "physiologic nystgamus." The role of the light source in testing is discussed, with special regard to the wavelength of light employed for the illumination of the object and of the background. The second portion of the treatise is to follow.

P. Thygeson.

Lombard, G. **Visual acuity in low illumination.** Arch. d'opht. **19**:730-763, Oct.-Nov., 1959.

This is the second portion of an exhaustive treatise on visual acuity in low illumination. In this portion there is detailed discussion of various factors affecting visual acuity, such as physiologic aberrations, chromatic aberration and diffraction, spherical aberration, and irregular deformities of the eye. Other subjects covered are the Stiles-Crawford effect, nocturnal myopia, and the possible

role of a dynamic lens. The role of color in nocturnal and crepuscular vision is fully discussed, as also the function of visual acuity as related to retinal topography. The author concludes with a statement that the scientific study of nocturnal vision must be based on an exact topographic map of the retina and on the precise function of each of its points. A valuable bibliography of 195 references is appended. (195 references)

P. Thygeson.

Vajda, P. **Physiologic-optic findings in a case of rod-monochromatism.** Szemeszet **96**:172-178, 1959.

As seen from the luminosity curve, fusion frequency and adaptation curve, so-called rod-monochromatism is characterized by the complete absence of the capacity to distinguish colors, nystagmus, decreased vision, and photophobia. The sight in these patients is mainly transmitted by the rods. However, the elevation of the luminosity curve at 600 mμ speaks in favor of the presence of primitive cones having no function in color vision, whilst the pathologic increase of the rod threshold points to the damage of rods at the same time.

Gyula Lugossy.

## 5

### DIAGNOSIS AND THERAPY

Best, F. **Localization during voluntary ocular movements.** Ophthalmologica **138**: 183-194, Sept., 1959.

On the basis of new observations (with a fixed or moving flickering light source in an otherwise dark room) the phenomenon of the objects of visual space remaining characteristically stationary during voluntary ocular movements is reanalyzed. A satisfactory interpretation and explanation is found in the concepts of cybernetics. (1 figure, 10 references)

Peter C. Kronfeld.

Heinzen, H. and Weuerth, A. **Stereogoniophotography.** Ophthalmologica **138**: 214-220, Sept., 1959.

The apparatus for stereo-goniophotography exhibited at the International Ophthalmological Congress in Brussels (September 1958) is described in detail. The basic part of the apparatus is an old Zeiss slitlamp to the oculars of which two microphotographic cameras with Leica backs are attached. The light source is an electronic flash adjustably mounted on a metal ring concentric with the anteroposterior axis of the slitlamp. Goldmann's three-mirrored contact lens gives access to the angle. (3 figures, 10 references)

Peter C. Kronfeld.

Hofmann, H. **The use of thrombin in ocular surgery.** Klin. Monastbl. f. Augenh. **135**:710-712, 1959.

The author reports his favorable experiences with topostatin drops and sponges (Hoffman-La Roche). Hemostasis is accelerated by the use of either drug. Furthermore, a fibrin film can be obtained by mixing topostatin with human plasma. This film provides good wound closure in perforating corneal injuries, cataract surgery, and keratoplasty. (5 references)

Gunter K. von Noorden.

Huysman, J. **Treatment of diplopia due to scar tissue.** Ophthalmologica **138**: 237-238, Sept., 1959.

The otherwise successful result of five operations for retinal detachment in the 30-year-old female patient was marred by almost complete loss of adduction of the left eye, the one which had been operated upon. With the right eye in primary position the left eye assumed a position of about six to ten degrees of exophoria and of six degrees of hyperphoria. For the correction of this condition the author performed the operation which he describes as follows: "Sutures were placed

under the tendon of the superior and lateral rectus. After injection of hyaluronidase and pulling gently for about 20 minutes I succeeded in adducting the left eye to such an extent that the cornea practically disappeared under the plica. The eye was fixed in a markedly adducted and depressed position for two and one half days. Two weeks later there was orthophoria in all directions. This favorable result has persisted up to the present moment." Peter C. Kronfeld.

Kanagasundaram, C. R. **Attachment for a Tudor Thomas corneal graft stand.** Brit. J. Ophth. **43**:504-506, Aug., 1959.

The author describes his attachment for holding donor corneas from eyes that have been evicerated after acute injuries. The excised donor cornea is firmly fixed near its periphery by a cap with an 11 mm. aperture in the cap. The intraocular pressure can be controlled during the cutting of the graft. (2 figures)

Irwin E. Gaynon.

Kozousek, V. **Clinical flicker perimetry.** Ophthalmologica **138**:195-214, Sept., 1959.

An accurately calibrated flickering light source mounted on the projection perimeter of Maggiore was the apparatus used in this very extensive study of the critical fusion frequency (CFF) in representative areas of the visual field. In early stages of hypertensive cardiovascular disease (Keith-Wagener stage I and II) the ratio of highest eccentric CFF to centric (macular) CFF appeared lower than in the controls. In various diseases of the optic nerve (including glaucoma) flicker perimetry gave definitely abnormal results at an earlier stage than the standard methods of perimetry. (15 figures, 20 references)

Peter C. Kronfeld.

Orlowski, W. and Obniski, J. **The use of controlled vascular hypotension in eye surgery.** Ophthalmologica **138**:264-273, Oct., 1959.

Ganglionic blocking agents added to the usual local anesthesia may facilitate operations such as dacryocystorhinostomies and major lid plastics in which bleeding from multiple small vessels is likely to ocur. (12 references)

Peter C. Kronfeld.

Osswald, R. **Microphotography of the living eye with the slitlamp.** Klin. Monatsbl. f. Augenh. **135**:697-705, 1959.

Pictures of the anterior ocular structures were taken with the Minox camera which was mounted on a Zeiss slitlamp. The author uses a broad beam for illumination and his technique permits photography not only of the anterior segment but also of anterior portions of the vitreous. The problems and limitations of slitlamp photography are discussed. (18 figures, 3 references)

Gunter K. von Noorden.

Pajor, R. **Experiences with the euthyscope.** Szemeszet **96**:160-164, 1959.

The author discusses the views on amblyopia and gives a historic outline of therapeutic methods. Then he reports 34 cases of his own. Results are tabulated. Cüppers' method is believed to be a useful means in the treatment of amblyopia. Results are particularly good under six years of age if other completing methods also are employed. Unlike other authors, Pajor obtained also some results with patients beyond the age of 12 years.

Gyula Lugossy.

Preziosi, V. **Diathermy electrode.** Brit. J. Ophth. **43**:502-503, Aug., 1959.

A new diathermy electrode is described. It has controlled negative pressure so that it can be applied to a soft eye as well. It also contains a suction tube to keep the scleral surface dry. It may be used where

direct vision is not possible. (1 figure)
Irwin E. Gaynon.

Schubert, H. **Hyperemic treatment in ophthalmology with Progresin.** Klin. Monatsbl. f. Augenh. **135**:717-719, 1959.

Progresin (Riedel- de Haën, Berlin) is a drug which causes mild and continued dilatation of the small arteries. The author successfully treated several cases of retrobulbar neuritis and juxtapapillary chorioretinitis by the oral administration of Progresin. Gunter K. von Noorden.

## 6

### OCULAR MOTILITY

Ayberk, Nejat. **Ocular torticollis with hypofunction of the superior oblique muscle.** Istanbul Göz Klinigi Bull. **5**(17): 146-150, Oct., 1959.

The author calls attention to the relative rarity of pure vertical squint and describes a case which resulted from hypofunction of the right superior oblique muscle and hyperfunction of the contralateral inferior rectus muscle. The disturbance of the function of these muscles led to torticollis and scoliosis. Resection of the right superior oblique muscle and retroplacement of the left inferior rectus muscle brought about proper alignment of the optic axes of the eyes not only in the primary position but in the other directions of gaze as well. The torticollis disappeared promptly. F. H. Haessler.

Huysmans, J. **Correction of cyclophoria.** Ophthalmologica **138**:238, Sept., 1959.

A 41-year-old female patient was operated on successfully for an early senile cataract in the right eye. Ten years later when the left eye had assumed a position of marked exotropia the patient requested an operation on the other eye. When the situation was explained to her, she agreed to have the cataract operation plus the necessary muscle operations.

After tenotomy of the left lateral rectus muscle and recession of the right lateral rectus, there remained a plus cyclophoria of the left eye of about 10 degrees. For the correction of this condition the author performed the following operation: "Sutures were placed under the tendons of the superior and inferior rectus muscles of the left eye. Hyaluronidase was injected subconjunctivally all around the globe. The eyeball could then be rotated easily into the position of over-correction of the existing cyclophoria. In that position the eye was immobilized for six days. Postoperatively there was a slight over-correction, that is minus cyclophoria. With the help of orthoptic training, the patient acquired satisfactory binocular vision. Peter C. Kronfeld.

Molnar, K. **The stereophorometer, a new instrument of orthoptic examination and treatment.** Szemeszet **96**:164-168, 1959.

The stereophorometer is an instrument for examining disorders of the equilibrium of the oculomotor muscles and binocular vision. Further it is useful in orthoptic therapy. Examinations are simple, quick, and precise, independent of distance and direction of gaze. In pleoptic and orthoptic therapy the instrument guarantees the cooperation of the squinting child. Gyula Lugossy.

Phillips, Calbert I. **Strabismus, anisometropia, and amblyopia.** Brit. J. Ophth. **43**:449-460, Aug., 1959.

Anisometropia per se does not cause strabismus. Anisometropic (disuse, suppression or accommodative) amblyopia occurs when the image in the affected eye is blurred and its size is different from that of the other eye. The ability of the peripheral retina to retain its binocularity explains the absence of squint. Full correction of the anisometropia is tolerated by children, myopes and presbyopes. Hy-

peropes prefer to have images of equal size. (28 references) Irwin E. Gaynon.

Scharf-Mayweg, S. **The treatment of strabismus in small children.** Ophthalmologica **138**:175-182, Sept., 1959.

This is a plea for the earliest possible treatment of concomitant squint, particularly of the non-alternating convergent type. In such cases the distinction between centric and eccentric fixation of the squinting eye is very important and can usually be made in children two years of age or older. Occlusion of the non-squinting eye may be tried for short periods and may result in a change from eccentric to centric fixation of the originally squinting eye. If this change does not take place or if the child is over two years of age at the inception of treatment, the author recommends occlusion of the squinting eye as the primary therapeutic move. This is certain to prevent the firm establishment of eccentric fixation and may, actually, change it to a centric one. The results in ten cases of this type are reported in some detail. Once central fixation by the originally squinting eye has been achieved this eye should be made the leading eye by careful occlusion of the opposite eye, keeping in mind the possibility of an amblyopia developing in that eye as the result of prolonged occlusion. Alternating occlusion and systematic instruction in conscious, willful alternation are the safest methods to maintain centric fixation and good acuity in each eye.

Eccentric fixation in children over five years of age requires systematic treatment by the afterimage method of Cueppers or the dazzling method of Bangerter.

Even alternators, until they are operated on, may benefit from alternating occlusion because there is a good chance of some degree of normal binocular vision having been present prior to the development of the squint. Once the diagnosis of alternation with good acuity in each eye is established and any existing accommodative factor has been corrected, surgery is indicated and should be performed early because of the better chances of attaining binocular sensory co-operation.

The very much rarer divergent strasbismus occurs in small children in two forms, as a divergence excess or a convergence insufficiency. Prevention of unilateral amblyopia is just as important as in convergent strabismus. (6 references)
Peter C. Kronfeld.

Sternberg, A. and Bohar, A. **Observations with the occlusive treatment of 109 excentrically fixating squinting eyes.** Szemeszet **96**:156-160, 1959.

Of 207 excentrically fixating, squinting amblyopic patients, 156 were treated by occlusion. In two thirds of excentrically fixating young children the occlusion of the good eye resulted in central fixation. In the opinion of the authors occlusion applied consistently at a young age is the best means of preventing and treating excentric fixation. Gyula Lugossy.

## 7

## CONJUNCTIVA, CORNEA, SCLERA

Alberth, B. **A new method of treatment for herpetic keratitis.** Ophthalmologica **138**:311-314, Oct., 1959.

The essential of the method is an almost penetrating circular incision of the cornea, made with a trephine of suitable size. The method was suggested to the author by the observation that the conventional lamellar keratoplasty almost immediately relieves the blepharospasm, photophobia and the ocular pain of severe herpetic keratitis. Compared to lamellar keratoplasty the circular incision of the cornea is technically easy, the operative risk is much smaller, and the optical results are better. The recovery period is

considerably shorter. The author has used the new method in 12 cases with gratifying results. Peter C. Kronfeld.

Ayberk, Nejat. **Differential diagnosis between Parinaud's syndrome and conjunctival tuberculosis.** Istanbul Göz Klinigi Bull. **5**(17):157-159, Nov., 1959.

The differentiation was made possible by biopsy and culture on Loewenstein-Nielsen medium. (5 figures)
F. H. Haessler.

Blatt, N. and Popovici, V. **Modified technique to fixate and cover the graft during corneal transplant procedure.** Klin. Monatsbl. f. Augenh. **135**:557-564, 1959.

A limbus-based rectangular conjunctival flap is mobilized, pulled over the graft, and anchored below the limbus to the conjunctiva with two long sutures. The flap cannot retract and the graft is held in place. The same technique is useful when temporary protective coverage of the cornea is desirable, such as in perforating ulcers, neuroparalytic keratitis, lagophthalmos, exophthalmos, and corneal anesthesia.
Gunter K. von Noorden.

Heydenreich, A. **Starlike suture for fixation of the graft in perforating keratoplasty.** Klin. Monatsbl. f. Augenh. **135**: 571-572, 1959.

An indirect preplaced suture is described which is uncomplicated and useful even in large grafts. (1 figure)
Gunter K. von Noorden.

Jochmus, H. **Contribution to the knowledge of alcaptonuria and ochronosis.** Klin. Monatsbl. f. Augenh. **135**:647-653, 1959.

A review of diseases causing discolorations in cornea, conjunctiva or sclera is given. Alcaptonuria belongs to the diseases which are caused by an inborn error of amino acid metabolism. The case of a 65 year old woman is reported in detail. Therapy remains unsuccessful until the enzyme is discovered which converts homogentisic acid into acetoacetic acid. (3 figures, 24 references)
Gunter K. von Noorden.

Mataur, S. P. **Amniotic membrane in the treatment of corneal ulcers.** Ophthalmologica **138**:307-310, Oct., 1959.

Once a serpentic ulcer of the cornea has been made regressive by anti-infective measures the healing process may be accelerated by covering the ulcer with small pieces of specially prepared and autoclaved human amniotic membrane. The method of preparation makes the membrane stick to the affected area for several hours. Within 24 hours the membrane usually disintegrates. The treatment is repeated every day for four to six days. Peter C. Kronfeld.

Mathur, S. P. **Conjunctival plasmoma.** Brit. J. Ophth. **43**:499-500, Aug., 1959.

Two cases of plasmoma of the palpebral conjunctiva are described. (4 references)
Irwin E. Gaynon.

Palich-Szántó, O. **The avascular form of interstitial keratitis.** Klin. Monatsbl. f. Augenh. **135**:719-724, 1959.

Two cases of an extraordinarily mild type of interstitial keratitis are reported. Ciliary injection was mild or almost absent. Syphilitic etiology must still be suspected in all cases of deep keratitis. The author assumes that modern antiluetic therapy results in diminished toxicity of the spirochete, and thus in the manifestation of a milder form of interstitial keratitis. (14 references)
Gunter K. von Noorden.

Zintz, R. and Vivell, O. **Clinical and etiologic features of epidemic keratoconjunctivitis.** Klin. Monatsbl. f. Augenh. **135**:521-533, 1959.

Serologic examinations with the ade-

novirus complement fixation test and with a specific neutralization test for adenovirus type 8 were performed in 50 patients with typical epidemic keratoconjunctivitis, and in 20 patients with the atypical form of this disease. A significant increase of complement fixating antibodies, as well as increase in titer with the neutralization test for adenovirus type 8, were present in most of the cases with the typical form of the disease. Positive serologic results were only rarely found in patients with the atypical form. Reports from other countries are accumulating which indicate that adenovirus type 8 can be isolated from typical epidemic keratoconjunctivitis. The epidemiology of the disease is discussed. The significance of the conjunctiva as the site of entry for various virus types is emphasized. (3 tables, 30 references)

Gunter K. von Noorden.

## 8

## UVEA, SYMPATHETIC DISEASE, AQUEOUS

Correa Meyer, I. **Degenerative processes of the choroid and retina.** Arq. brasil. de oftal. **22**:60-85, 1959.

See abstract in section 11. Retina and vitreous.

Gamringer, H., Schreck, E. and Wollensak, J. **Pathogenesis and therapy of anular exudative pseudotumerous cyclitis.** Klin. Monatsbl. f. Augenh. **135**:638-646, 1959.

Four patients with this disease have been observed by the authors. Another name for the condition is "spontaneous serous anterior choroidal detachment." In the reported cases both eyes were involved and a circumferential choroidal detachment was present in the extreme periphery. This was accompanied by acute or subacute cyclitis, serous retinal detachment, disseminated choroiditis or papillitis. Rheumatic or tuberculous allergic factors seem to be of etiologic significance. In view of these considerations, the authors recommend the use of Prednisolone orally. (1 figure, 32 references)

Gunter K. von Noorden.

Puscariu, E. **Sympathetic ophthalmia and the possible nature of its still undetermined cause.** Arch. d'opht. **19**:631-633, Sept., 1959.

The author comments on theories of etiology in sympathetic ophthalmia and notes certain resemblances between this disease and trachoma, particularly the long incubation period and the chronic nature with remissions and relapses. She suggests that the causal agent may belong to the same general type of infectious agent.

P. Thygeson.

Staehelin, A. **Catamnestic studies following uveitis.** Klin. Monatsbl. f. Augenh. **135**:659-669, 1959.

Catamnestic studies in 87 patients who were treated for endogenous uveitis between 1932 and 1936 revealed the following results: 1. life expectancy was on the average 4⅓ percent less than in the general population. 2. tuberculosis was a relatively frequent autopsy finding, 3. 50 percent of the patients who were reexamined gave a history of rheumatic disease at one time or another, 4. generally, the morphologic and functional condition of the eyes had improved on reexamination, and 5. cataract and secondary glaucoma occurred in 16.5 percent of the surviving group. On the other hand, there was a higher incidence (27 percent) of secondary glaucoma in the group of patients that died.

Uveitis is a symptom of a general disease which, as shown in this study, can decrease the life span of patients considerably. The study did not furnish the expected contribution to the etiology of uveitis. (3 tables, 34 references)

Gunter K. von Noorden.

Vannas, S. **Prognosis of malignant tumors of the choroid.** Klin. Monatsbl. f. Augenh. **135**:678-690, 1959.

Beteween 1925 and 1955 the author observed 141 patients with malignant melanoma of the choroid, five patients with metastatic melanoma in one or both eyes, and one patient with carcinomatous metastases of the uvea. The surviving patients were re-examined. The cause of death was ascertained in the others. The majority of the patients had enucleations and had received post-operatively a total X-ray dosage of 5000 to 6000 r to the orbit, in daily doses of 350 r. The five year follow-up revealed a mortality of 28 percent, the ten year follow-up of 51 percent, and after 20 years 54 percent of the patients had died from metastases. These figures compare favorably with other statistics and support the belief that intense irradiation following early surgery may be effective in prolonging the life of patients with malignant uveal melanomas. A larger number of patients, however, must be evaluated before the value of post-operative X-ray treatment becomes firmly established. Hormonal treatment and effects of hypophysectomy in patients with intraocular metastatic carcinoma are briefly discussed. (1 figure, 5 tables, 31 references)

Gunter K. von Noorden.

## 9

### GLAUCOMA AND OCULAR TENSION

Biro, I. **Observations concerning hereditary glaucoma.** Ophthalmologica **138**: 161-169, Sept., 1959.

The author's rather sketchy observations point out the clinical variability of hereditary glaucoma in children of the same family. Infantile glaucoma made its appearance with enlargement of the anterior segment in the oldest sibling in one family and without such enlargement in two younger siblings. In another family adult glaucoma with congestive symptoms occurred in some of the siblings and without them in others. (1 figure, 19 references) Peter C. Kronfeld.

Eggink, E. **Preliminary report on routine tonometry in one thousand patients over forty years of age.** Ophthalmologica **138**:225-230, Sept., 1959.

A tonometric reading of six or less scale units with a certified Schiøtz tonometer and a 7.5 gm. weight was considered as "suspicious." At the first tonometric examination 97 out of 1,000 individuals over forty years of age who visited the out-patient department (for unstated reasons) gave a suspicious reading. Re-examination of these patients reduced the number of suspicious readings to 45 and in 23 of these the diagnosis of glaucoma was made on the basis of a "pathologic pressure curve," associated in 15 patients with pathologic field findings and in 12 patients with pathologic disc findings. Peter C. Kronfeld.

Evans, E. M. and Klein, M. **A bulbar suction test for glaucoma.** Brit. J. Ophth. **43**:494-498, Aug. 1959.

A Kukán ophthalmodynamometer is applied to the sclera near the outer canthus. A negative pressure of 150 mm. Hg is induced. The ocular tension (Schiøtz weightless) is recorded. The pressure is raised to 165 mm. Hg for four minutes. At this time the pressure is reduced to 150 mm. Hg and the tension is again recorded. The results in normal controls and in glaucoma are compared. (3 figures, 4 references) Irwin E. Gaynon.

Kuechle, H. **Reactive and regulatory fluctuations of the intraocular pressure.** Ophthalmologica **138**:254-263, Oct., 1959.

In previous papers the author has dealt with the effects of electroshock on intraocular pressure (cfr. Am. J. Ophth. 46: 615, 1958). The present paper stresses the

complexity of the mechanisms whereby electroshock causes such changes. The primary and principal effect is that of stimulation of the hypothalamus which probably entails a direct stimulating effect upon the center for intraocular pressure regulation, resulting in a sharp rise in pressure. Then there are more indirect pathways via the parasympathetic on the one hand, and via the pituitary on the other. Finally the cortically elicited convulsions influence the intraocular pressure in a still not entirely clarified manner. Some of these mechanisms have to be considered as regulatory, compensatory processes. Failure of these mechanisms may be an essential factor in some of the glaucomas. (1 figure, 35 references) Peter C. Kronfeld.

Lavergne, G. **Postoperative changes in ocular rigidity.** Ophthalmologica **138**: 169-174, Sept., 1959.

The ocular rigidity of human eyes, as estimated by repeated, paired tonometric readings, is temporarily lowered by lens extractions, diathermy or scleral resection operations for retinal detachment, and iridencleises, if the latter lead to voluminous blebs. (3 tables, 15 references) Peter C. Kronfeld.

Leydhecker, W. **Difficulties in determinations of scleral rigidity with the Schiøtz tonometer.** Klin. Monatsbl. f. Augenh. **135**:669-678, 1959.

Tonometers are calibrated for eyes with average rigidity. Clinically the rigidity can be determined tonometrically after Friedenwald. The intraocular pressure is determined with the 5.5 gm. and the 10 gm. weight. If these scale readings are known, the rigidity coefficient can be read off directly from Friedenwald's nomogram. The rigidity coefficient (K) is constant for a certain eye and independent of intraocular pressure but shows individual differences.

The author measured the ocular tension with two weights in 1,497 eyes of patients with healthy eyes. Tonometry had been performed in all patients at an earlier date and revealed that none of these subjects had an intraocular pressure of more than 20 mm. Hg. K was determined with Friedenwald's nomogram. The most frequent value for K was 0.0178, the mean value was 0.0240. This unequal distribution of values was impressive. It is explained by the fact that on the calibration tables for the 1955 tonometer the mm. Hg values given for the 5.5 gm. and the 10 gm. weight do not exactly correspond with each other in the range of 0.5 unit scale readings. The introduction of such scale reading errors is analyzed and demonstrated by tables. No conclusions can be drawn from single measurements. Repeated determination of the rigidity is essential if one uses Friedenwald's method. The same applies to applanation tonometry. (12 figures, 4 tables, 13 references) Gunter K. von Noorden.

Valu, L. **Observations with new fistula-forming operations.** Szemeszet **96**: 178-183, 1959.

Observations with Scheie's goniopuncture and Preziosi's procedure are described. Goniopuncture is a simple, short-lasting intervention which is free from danger. The author applied it to eight eyes of five patients with good results. It should be preferred to other methods of fistulizations in eyes with hydrophthalmos, especially because the outlook for a second operation is not worse if goniopuncture is unsuccessful. Prezionsi's operation was carried out as a second or third operation and its use is suggested if other operations have failed.

Gyula Lugossy.

Valu, L. **Glaucoma in myopic eyes.** Ophthalmologica **138**:302-307, Oct., 1959.

The anatomic peculiarities of the

markedly nearsighted eye alter the course of chronic simple glaucoma to the extent of the appearance and wide acceptance in the ophthalmological literature of the term "myopic glaucoma." One pertinent case is reported in detail, unfortunately without actual measurements of the ocular rigidity. (2 figures, 5 references) Peter C. Kronfeld.

## 10

### CRYSTALLINE LENS

Ayberk, Nejat. **Enzymatic zonulolysis.** Istanbul Göz Klinigi Bull. **5**(17):151-156, Nov., 1959.

The author reviews the current literature on the subject with particular emphasis on the complications which led him to conclude that the action of α-chymotripsin on the zonule is striking in the older patients with cataract but is distinctly less effective in the young. Extracapsular delivery of the lens and vitreous loss occur twice as frequently as in operations done without this substance. Cicatrization is not retarded. The postcorneal deposition of pigment is ascribed to injury of the iris tissue during the introduction of the canula. (1 table, 21 references) F. H. Haessler.

Coop, D. H. **Removal of Elschnig's pearls.** Brit. J. Ophth. **43**:501, Aug., 1959.

Elschnig's pearls occluded the pupils of a 25-year-old man whose lamellar cataracts had been needled. The pearls were removed by irrigation through a keratome incision with good results. (1 figure) Irwin E. Gaynon.

Csillag, F. **Intracapsular cataract extraction by tumbling with horizontal grip on the capsular fold. Capsule forceps for horizontal grip of the capsular fold.** Klin. Monatsbl. f. Augenh. **135**:565-570, 1959.

The capsular traction zones are distributed over a larger area if the capsule can be grasped horizontally. This would make rupture of the capsule during extraction less likely. The author describes a curved capsule forceps for this purpose. The usefulness of the instrument could be demonstrated in 100, mostly intracapsular, cataract extractions. (5 figures, 1 table, 12 references) Gunter K. von Noorden.

Dobree, J. H. **Scalpel and scissors.** Brit. J. Ophth. **43**:513-520, Sept., 1959.

A new technique is described for making the section and inserting sutures for cataract extraction. A wide limbus-based conjunctival flap is brought down over the cornea. A vertical groove is then made halfway around the limbus and extending through two-thirds of the thickness of the sclera. The corneal lamellae are then split over the limbus by sharp dissection after three corneo-scleral sutures have been put in place through the groove. The chamber is then entered almost vertically through the posterior lamella of the cornea and this incision completed by scissors. A small superior iridotomy is made at the base above by pulling the iris forward. After delivery of the lens the sutures are pulled tight and the conjunctival flap is sutured separately. This method has been used in 120 cases and is recommended because there are fewer complications. (3 figures, 1 reference) Morris Kaplan.

Phillips, C. I. **Buried mattress suture for cataract incisions.** Brit. J. Ophth. **43**:572-573, Sept., 1959.

Phillips briefly describes a single buried mattress suture in cataract surgery using a 15-0 five-strand Spanish silk suture. The suture is placed so that the knot is buried behind the limbus beneath a broad limbus-based flap. (1 figure, 3 references) Morris Kaplan.

## 11

### RETINA AND VITREOUS

Biro, I. **Symmetrical development of pigmentation as a specific entity in the fundus pattern of pigment degeneration of the retina.** Szemeszet **96**:168-171, 1959.

Certain forms of chorioretinitis cannot always be distinguished from degeneratio pigmentosa. The author claims, on the basis of his large material, that the symmetrical development of pigmentation is a specific characteristic of retinitis pigmentosa. The claim is demonstrated by numerous examples.

Gyula Lugossy.

Correa Meyer, I. **Degenerative processes of the choroid and retina.** Arq. brasil. de oftal. **22**:60-85, 1959.

The author discusses at length the various heredo-degenerative diseases which affect the choroid and retina. Tapeto-retinal degenerations involve the pigment epithelium primarily, while the abiotrophies are characterized by a disintegration of the rods and cones. A comparison is made of the abiotrophic retinoses, which may be peripheral in location (retinitis pigmentosa) or central (macular dystrophy). Heredo-constitutional diseases arise in the neuroepithelium and have the special feature of a cessation in evolution. In this category are congenital hemeralopia, color blindness and Oguchi's disease. The heredodegenerative diseases proper are those clinical entities which do not arise in either the pigment epithelium or the sensory neuro-epithelium. A schematic classification of the various degenerative diseases is presented.

James W. Brennan.

Hoffmann, R. **The so-called retinal artery embolism.** Klin. Monatsbl. f. Augenh. **135**:707-710, 1959.

Embolism of the superior temporal branch of the central retinal artery occurred in one patient. Only initial transient symptoms were present. The embolus disappeared slowly without therapy and caused no subsequent symptoms in spite of the fact that it remained visible ophthalmoscopically for a considerable length of time. (3 references)

Gunter K. von Noorden.

Munro, S. **Fundus appearances in a case of a acute dermatomyositis.** Brit. J. Ophth. **43**:548-557, Sept. 1959.

Acute dermatomyositis is a not uncommon collagen disease in which eye pathology has been reported quite rarely. The case which the author reports is one of only six since the original description. The disease is characterized by great and progressive muscular weakness and fatigability and has a mortality rate of 40 to 50 percent. A 10-year-old boy was hospitalized with the typical picture of the disease but with vision reduced to counting of fingers in each eye. He had massive white exudates throughout the retina and worse in macular areas. There were numerous hemorrhages both superficial and deep with marked attenuation of the vessels. He was given high doses of Prednisolone with steady improvement generally but ophthalmologically progressive optic atrophy developed with vision reduced to 6/60 in each eye. This fundus picture closely resembles that seen in systemic lupus erythematosus and scleroderma. (8 figures, 16 references)

Morris Kaplan.

Sabbadini, D. **The medico-surgical prophylaxis of idiopathic detachment of the retina.** Arch. d'opht. **19**:620-630, Sept., 1959.

Sabbadini reviews current concepts of the role of heredity in predisposing to idiopathic retinal detachment, with particular reference to myopia. He discusses the possibility of preventing chorioretinal

changes in myopia by giving attention to general health measures. He then reviews indications for prophylactic surgery in impending detachment, particularly in cases with retinal tears. He discusses the various types of surgery to be employed, warns against the use of any perforating procedure, and concludes by reporting 14 illustrative cases of his own.

P. Thygeson.

Sverak, J. Peregrin, J. and Hradecky, F. **Electroretinographic study of retinal metabolism.** Ophthalmologica **138**:287-291, Oct., 1959.

The ERG of a 52-year-old male patient with suspected tapetoretinal degeneration improved, that is, the b-wave increased temporarily under the influence of a large dose of glucose by mouth. Tests of this kind may give information about the degree of possible reversibility of retinal pathologic processes. (9 references)

Peter C. Kronfeld.

## 12

### OPTIC NERVE AND CHIASM

Badtke, G. **Size anomalies of the optic nerve head with special consideration of black megalopapilla.** Klin. Monatsbl. f. Augenh. **135**:502-510, 1959.

Hyperplasia of the optic disc is less frequently seen than hypoplasia. A case of unilateral megalopapilla is reported and compared with a similar case published by Franceschetti and Bock. A survey of the various size anomalies of the optic disc is given. This discloses that a teratologic sequence can be established which extends from coloboma of the disc, via megalopapilla, normal disc, hypoplastic disc, to aplasia of the nerve head. Anomalies of the anlage of the primary epithelial papilla seem to be the etiologic basis for all these malformations. (1 figure, 5 references)

Gunter K. von Noorden.

## 13

### NEURO-OPHTHALMOLOGY

Cameron, M. E. **Lesions of the ciliary ganglion as a cause of Argyll Robertson and Adie pupils.** Brit. J. Ophth. **43**:471-476, Aug., 1959.

The author reports a case of Adie pupil following herpes zoster ophthalmicus. The pupil was irregularly dilated, indicating a lesion of the sphincter. The convergence reaction returned after a period of ten months. The reaction to light remained absent. This is explained by the presence of a synapse in the ciliary ganglion for light reaction but none for near. The marked response to neosynephrine and cocaine show that the sympathetic fibers and the dilator muscles are intact. The sensitization to mecholyl indicates postganglionic destruction of the parasympathetic pathways. If the light fibers are destroyed, an Argyll Robertson pupil results. (7 references)

Irwin E. Gaynon.

Zagora, E. **Observations on the evolution and neurophysiology of the co-ordinations between eyes and limbs.** Ophthalmologica **138**:249-254, Oct., 1959.

The theme and the general character of this study is clearly stated in the author's introduction: "The newborn infant during his postnatal development, like the human species in the course of biological evolution, achieves a mastery in reaching for and grasping the visually perceived objects. The developmental changes which the co-ordination between eyes and limbs undergoes in its progress toward maturity in the course of ontogenesis of infant behavior reflect to a certain extent the course of maturation of the central nervous system." The author's data are mostly observations by means of psychologic methods. What he establishes are chiefly chronologic sequences and general patterns in the de-

velopment of the relationships between visual perception and motor function of the extremities. (4 references)

Peter C. Kronfeld.

## 14

### EYEBALL, ORBIT, SINUSES

Bushe, K.-A. **Differential diagnosis of unilateral exophthalmos.** Klin. Monatsbl. f. Augenh. **135**:465-486, 1959.

Unilateral exophthalmos is divided into three groups, namely inflammatory, bland and non-pulsating, and pulsating. Acute inflammatory exophthalmos may be secondary to purulent sinusitis. Pseudotumor, mucocele, and syphilitic granuloma lead to chronic inflammatory exophthalmos. In the second group the author differentiates between exophthalmos dues to systemic disease and that caused by localized orbital disease. The various etiologic factors are discussed. Vascular disease and bony orbital defects cause pulsating exophthalmos. The differential diagnosis of vascular lesions is discussed. The diagnostic value of thorough external examination in connection with general physical examination, skull films, and orbital films is stressed. EEG and angiography are further diagnostic aids. (39 figures, 3 tables, 13 references)

Gunter K. von Noorden.

Gärtner, J. **Orbital involvement in Brill-Symmers disease.** Klin. Monatsbl. f. Augenh. **135**:486-496, 1959.

This chronic disease is characterized by enlargement of solitary or grouped lymphnodes of the cervical, axillary, thoracic, abdominal, and inguinal regions. Splenomegaly is present in 33 percent of the cases, the blood picture is essentially normal, and the sedimentation time is elevated. Two cases with orbital involvement are reported. The pathologic findings are discussed in the light of a possible neoplastic nature of the disease. Formation of pseudofollicles in the course of lymphatic neoplasia may occur even in areas where lymph nodes are normally absent. (5 figures, 23 references) Gunter K. von Noorden.

## 15

### EYELIDS, LACRIMAL APPARATUS

Aczél, G. **Skin grafts of both lids with a single intermediary flap.** Klin. Monatsbl. f. Augenh. **135**:573-574, 1959.

Large skin defects following burns involved the upper and lower lid and the inner canthus. These areas were grafted with a single flap. The graft took well and yielded satisfactory cosmetic and functional results. (2 figures, 4 references) Gunter K. von Noorden.

Bauer, F. **A new method of dacryocystorhinostomy.** Klin. Monatsbl. f. Augenh. **135**:575-577, 1959.

A modification of Fazaka's method is described. The inferior aspect of the lacrimal sac is sutured to the periosteum and to the nasal mucosa. This procedure has been successful in 14 cases. (4 figures, 2 references) Gunter K. von Noorden.

Bauer, F. **Reunion of traumatically disrupted lacrimal canaliculi.** Klin. Monatsbl. f. Augenh. **135**:706-707, 1959.

Surgical thread on a round needle is inserted through the punctum into the distal segment and from there into the proximal segment of the canaliculus. The threaded needle is then brought out through the skin from the anterior wall of the lacrimal sac. The suture can be removed in 10 or 12 days. This material is preferred to metal wire or plastic tube, both of which may cause discomfort to the patient, as well as tissue damage by pressure or irritation. (1 figure, 5 references) Gunter K. von Noorden.

# NEWS ITEMS

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News items should reach the editor by the 10th of the month. For adequate publicity, notice of postgraduate courses and meetings should be received three months in advance.

## ANNOUNCEMENTS

### RESEARCH MEETING

The official opening of the 29th annual session of the Association for Research in Ophthalmology, Inc., will be on Monday, June 13th, with Dr. James H. Allen, chairman, Board of Trustees, presiding, in the Mona Lisa room of the Eden Roc Hotel, Miami, Florida. Papers to be presented at the first session include: "The measurement of rabbit ciliary epithelial potentials in vitro," James E. Miller, and Marguerite A. Constant, Saint Louis, discussion to be opened by Albert M. Potts; "The transport of organic anions by the rabbit ciliary body: I. In vitro iodopyracet (Diodrast) accumulation," Bernard Becker, Saint Louis, discussion to be opened by V. Everett Kinsey; "The transport of organic anions by the rabbit ciliary body: II. In vivo transport of iodopyracet (Diodrast)," Max Forbes and Bernard Becker, Saint Louis, discussion to be opened by V. Everett Kinsey; "Diabetic retinopathy," J. Reimer Wolter, Ann Arbor, Michigan, discussion to be opened by B. S. Fine.

"The morphology of the vitreous body," B. S. Fine and A. J. Tousimis, Washington, D.C., discussion to be opened by George K. Smelser; "Visual pigment concentration and the electroretinogram," John E. Dowling, Cambridge, Massachusetts, discussion to be opened by Werner K. Noell; "The role of macular function in the ERG of monkey and man," J. H. Jacobson, H. T. Najac, and G. F. Gestring, New York, discussion to be opened by A. D. Ruedemann, Jr.; "Experimental malignant melanoma of the iris in the Syrian golden hamster," and Robert P. Burns and F. Fraunfelder, Portland, Oregon, discussion to be opened by John S. McGavic.

On Tuesday, June 14th, the program will include: "Observations on experimental trachoma produced in cynamolgus monkeys by elementary body virus strains propagated in yolk sac," P. Thygeson, D. Dawson, L. Hanna, and M. Okumoto, San Francisco, discussion to be opened by Alson E. Braley; "The effect of cortiosteroids on acute experimental ocular toxoplasmosis," Herbert E. Kaufman, Boston, discussion to be opened by Ralph W. Ryan; "Corneal destruction of extracts of cephalosporium mycelium," C. D. Burda, E. Fisher, Jr., New Orleans, discussion to be opened by Albert P. Ley; "Studies on experimental ocular drug hypersensitivity," A. M. Silverstein, S. Welter, L. E. Zimmerman, Washington, D.C., discussion to be opened by Phillips Thygeson.

"The rapid and convenient detection of toxoplasma antibodies using formalized human red cells," Herbert E. Kaufman, Boston, discussion to be opened by Seymour P. Halbert; "The regulation of the intraocular pressure in the cat's eye," Maurice E. Langham, Baltimore; discussion to be opened by Ludwig von Sallman; "The scleral rigidity function," M. G. Holland, J. Madison, and W. Bean, New Orleans, discussion to be opened by Elmer J. Ballintine.

On Wednesday morning, June 15th: "Nutritional and endocrine influences on the synthesis of albuminoid in rat lenses: II. The effect of pituitary hormones and of testosterone on the albuminoid synthesis in rat lenses," Zacharias Dische and Ginevra Zelmenis, New York, discussion to be opened by P. J. Leinfelder; "Resolution of phenol sulfokinase and phenol sulfatase in beef cornea by cellulose anion-exchanger; Chromatography," B. Wortman and A. Schneider, Saint Louis, discussion to be opened by J. Winston Barber; "The effect of oxygen tension on glucose uptake by the isolated rabbit lens," R. P. Lewis, Portland, Oregon, J. E. Harris, Minneapolis, and E. L. Talman, Portland, discussion to be opened by Carl Wachtl; "Photosensitization of proteins by methylene blue: II. Alteration of malic and lactic dehydrogenase activity of rabbit lenses," W. L. Fowlks, Minneapolis, discussion to be opened by Marguerite A. Constant.

"On the evolution of lens proteins," W. Manski, T. Auerbach and S. P. Halbert, New York, discussion to be opened by Carl Wachtl; "A critique of time amplitude ultrasonography," Gilbert Baum, Port Chester New York. Sir Stewart Duke-Elder, London, will receive the Proctor Medal at the awards banquet on Wednesday evening.

The final session, on Thursday morning, will include these papers: "Effect of plasma on glucose uptake by isolated rat lenses," T. G. Farkas, R. F. Ivory and S. J. Cooperstein, Cleveland, Ohio, and J. W. Patterson, Nashville, Tennessee, discussion to be opened by D. Venkat Reddy; "Content and distribution of ribonucleic acid in rat lenses in relation to age and cataract formation," Anima Devi and Zacharias Dische, New York, discussion to be opened by John F. R. Kuck, Jr.; "Further studies on corneal transparency," A. M. Potts, Chicago, and B. Friedman, Cleveland, discussion to be opened by John E. Harris; "The effect of endothelium on corneal wound healing, experimental study," James E. McDonald, Chicago, discussion to be opened by Frederick W. Stocker; "The ultrastructure of Bowman's membrane," Jack Kayes and Åke Holmberg, Saint Louis, discussion to be opened by George D. Pappas; "The enigma of typical monochromacy," Mathew Alpern and Harold F. Falls, Ann Arbor, discussion to be opened by Gordon L. Walls. The

Friedenwald Memorial Lecture will be given by Irving H. Leopold, Philadelphia.

### Home study courses

The 1960-1961 Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, which are offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on September 1st and continue for a period of 10 months. Detailed information and application forms can be obtained from Dr. William L. Benedict, the executive secretary-treasurer of the academy, 15 Second Street S. W., Rochester, Minnesota. Registrations should be completed before August 15th.

### Keratoplasty course

A new course on keratoplasty in all its aspects, including instruction in technique, will be presented at Presbyterian Hospital and Medical Center of San Francisco (formerly Stanford Hospital in San Francisco) on May 18th, 19th, and 20th, under the supervision of Dr. Max Fine. The fee is $100.00; enrollment limited. Write to Secretary, Eye-Bank, 2018 Webster Street, San Francisco 15, California.

### Orthoptic examination

The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in August and October, 1960.

The written examination will be nonassembled and will take place on Thursday, August 18th, in certain assigned cities and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, October 8th, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the Chairman of Examinations, Dr. Frank D. Costenbader, 1605 22nd Street, N.W., Washington 8, D.C., and must be accompanied by the examination fee of $30.00. Applications will not be accepted after July 1, 1960.

### Illinois meeting

The 34th convention of the Central Illinois Society of Ophthalmology and Otolaryngology will be held at the Illinois Hotel at Bloomington, Illinois, on April 22nd, 23rd, and 24th. The guest speakers will be Dr. John W. Henderson, Rochester, Minnesota, in ophthalmology, and Dr. Z. Z. Godlowski, Chicago, in otolaryngology. The society member speakers will be Dr. W. A. McNichols, Dixon, in ophthalmology, and Dr. George H. Woodruff, Joliet, in otolaryngology. Prof. Arthur W. Watterson, of the Geography Department, Illinois State Normal School, Bloomington, will be the speaker at the Saturday evening banquet.

### Papers for Southern Medical meeting

The Section of Ophthalmology and Otolaryngology of the Southern Medical Association announces that papers by physicians of either specialty living in the area of the Southern Medical Association are now being accepted for consideration for presentation at the next annual meeting to be held in Saint Louis, Missouri, from October 31st to November 3rd. The paper or an abstract of the paper should be sent directly to the secretary, Dr. Albert C. Esposito, Suite 1212, First Huntington National Bank Building, Huntington, West Virginia, as soon as possible.

## Miscellaneous

### To honor Dr. Calhoun

A $500,000 gift has been presented to the Emory University School of Medicine to establish a professorship in ophthalmology in honor of Dr. Phinizy Calhoun, distinguished Atlanta opthalmologist. The endowment came from friends of Dr. Calhoun who wished to remain unidentified.

Henry L. Bowden, chairman of Emory's Board of Trustees, said the gift "will permit further significant development in ophthalmology through direct support of professional leadership."

Tribute to Dr. Calhoun was paid in the board's resolution naming the professorship the "F. Phinizy Calhoun Chair of Ophthalmology."

### Symposium on structure of eye

Academic Press, New York, will publish the *Transactions* of the "Symposium on structure of the eye," which was part of the program of the International Congress of Anatomists held recently in New York. Dr. George K. Smelser, professor of anatomy, Columbia University, College of Physicians and Surgeons, was chairman of this section of the program.

The first session of the symposium was held at the Statler-Hilton Hotel, New York, on Monday afternoon, April 11th. Subsequent sessions, on Tuesday and Wednesday, April 12th and 13th, were held at the Columbia University Medical Center. The symposium included the following papers:

*Retina.* "Electron microscopy of the retina," Prof. Fritiof S. Sjöstrand, Director of the Laboratory for Biological Ultrastructure Research, Karolinska Institutet, Stockholm, Sweden; "Ultrastructure of photoreceptors," Prof. Dr. E. De Robertis and Dr. A. Lasansky, Instituto de Anatomia General y Embriologia, Facultad de Ciencia Médicas, Buenos Aires, Argentina; "The fine structure of vertebrate and invertebrate photoreceptors as revealed by low-temperature electron microscopy," Dr. H. Fernández-Morán, Head, Mixter Laboratories for Electron Microscopy, Neurosurgical Service, Massachusetts General Hospital, Boston, and Department of Biology, Massachusetts Institute of Technology, Cambridge; "Localization of oxidative enzyme systems in rat and chick retina in different physiologic states," Dr. A. G. Everson Pearse, Postgraduate Medical School, London; "The fine structure of the pigment epithelium in the turtle eye," Dr. Eichi Yamada, Professor of anatomy, School of Medicine, Kurume University, Kurume, Japan; "The effect of vitamin-A deficiency on the fine structure of retinal elements," John E. Dowling, and I. R. Gibbons, The Biological Laboratories, Harvard University, Cambridge; "General discussion of retinal structure in

relation to the visual process," Prof. George Wald, Biological Laboratories, Harvard University, Cambridge.

*Retina and Lens.* "Silver carbonate techniques for the demonstration of ocular histology," Dr. J. Reimer Wolter, University of Michigan Medical Center, Ann Arbor; "Functional architecture of the retinal epithelium," Dr. Maurice H. Bernstein, Department of Anatomy, Wayne State University, Detroit; "Histochemical observations on the enzymes of the retina," Prof. Olavi Eränkö, Mikko Niemi and Esteri Merenmies, Department of Anatomy, University of Helsinki, Helsinki, Finland; "A structural model for a retinal rod," Dr. J. J. Wolken, University of Pittsburgh, School of Medicine and Biophysical Research Laborary, Eye and Ear Hospital, Pittsburgh; "Comparative anatomy of the mammalian retina with respect to the electroretinographic response to light," Dr. Katherine Tansley, Institute of Ophthalmology, London; "The development and histochemistry of the pecten oculi," Prof. Ronan O'Rahilly and Dr. David B. Meyer, Department of Anatomy, Wayne State University, Detroit; "Cell surfaces in the crystalline lens," Dr. Theodor Wanko and Mary Ann Gavin, Ophthalmology Branch, National Institutes of Health, Bethesda, Maryland.

*Lens and vitreous humor.* "Morphologic development of the lens in relation to antigenic properties," Prof. Jan Langman, Department of Anatomy, McGill University, Montreal, Canada; "Recovery from and protection against radiation damage to the lens," Dr. Antoinette Pirie, Director, Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, England; "Lens antigens in relation to evolution," Prof. Seymour P. Halbert, Dr. W. Manski, and T. Auerbach, Department of Ophthalmology, Columbia University, New York; "The distribution of DNA synthesizing cells in lens epithelium following injury," Prof. Clifford V. Harding, Carl Feldherr, and D. B. Srinivasan, Departments of Ophthalmology and Physiology, Columbia University, New York; "Electron microscopic observations of the human vitreous body," Prof. Dr. W. Schwarz, Leiter der Forschungsabteilung für Elektronenmikroskopie, Freie Universität Berlin, Berlin; "Molecular morphology of the vitreous body," Dr. Endre A. Balazs, associate director, Retina Foundation, Boston.

*Trabecular meshwork and cornea.* "Structure of the filtration angle," Dr. Frantisek Vrabec, 1st Eye Clinic, University of Prague, Czechoslovakia; "The morphology and pathology of the trabecular meshwork: Special concern given to the problem of resistance to outflow," Prof. Dr. Johannes W. Rohen and H.-H. Unger, Anatomisches Institut der Universität, Mainz, Germany; "The fibrous components of the cornea," Dr. Marie A. Jakus, Retina Foundation, Boston; "Descemet's membrane in the human peripheral cornea: A study by light and electron microscopy," M. L. Feeney and Dr. L. K. Garron, Francis I. Proctor Foundation for Research in Ophthalmology and Department of Ophthalmology, University of California School of Medicine, San Francisco; "The use of permeability studies in the investigation of submicroscopic structure," Dr. David Maurice, Institute of Ophthalmology, London; "Electron microscopic studies of the fibrillogenesis in the human cornea," Prof. Dr. W. Schwarz, Leiter der Forschungsabteilung für Electronenmikroskopie, Freie Universität Berlin, Berlin; "The development of the structural and optical properties of the cornea," Prof. Alfred J. Coulombre and J. L. Coulombre, Department of Anatomy, Yale University School of Medicine, New Haven; "Tissue interaction and differentiation in the corneal and scleral stroma," Dr. Heinz Hermann, Department of Zoology, Institute of Cellular Biology, The University of Connecticut, Storrs, Connecticut.

*Iris, ciliary body, development.* "Electron miscroscopy of the pigment epithelium of the iris," A. J. Tousimis and Dr. Ben S. Fine, Armed Forces Institute of Pathology, Washington, D.C.; "The fine structure of the ciliary epithelium in relation to aqueous secretion," Prof. G. D. Pappas and Prof. G. K. Smelser, Departments of Ophthalmology and Anatomy, Columbia University, New York; "Electron microscope observations on the origin, development and genetic variation of melanin granules in the eye," Frank H. Moyer, Department of Biology, Johns Hopkins University, Baltimore; "Histogenesis of mouse retina studied with Thymidine-$H^3$," Dr. Richard L. Sidman, Laboratory of Cellular Neuropathology, Harvard Medical School, Boston; "Production of congenital eye malformations; Particularly in rat fetuses," Prof. H. Tuchmann-Duplessis and L. Mercier-Parot, Laboratoire d'Embryologie, Faculté de Médecine, Paris.

### Books for the blind

Books on records for the blind are available nationally in increasing quantity from two sources: the Library of Congress in Washington, D.C., and Recording for the Blind, Inc., at 121 East 58th Street, New York. The library puts out about 200 books a year, in 150 to 200 copies, mostly in the general or recreational field. Recording for the Blind, Inc., is strictly educational and will turn out about 850 books this year, in a much smaller number of copies, averaging nine or 10 apiece. Since these are educational books on continuous loan through the libraries serving the blind, this number of copies has so far proved sufficient.

The Recording for the Blind discs and the Library of Congress discs are both designed to be played on the Talking Book machine, or record player, obtainable without charge through the state agencies serving the blind. The Library of Congress uses a 33⅓ rpm recording speed, whereas Recording for the Blind uses 16⅔. At this slower speed, Recording for the Blind is able to get nearly an hour's reading on a small 7-inch disc, so that the recorded book takes up no more room than the printed copy. This is not only convenient for the student but has an advantage for the distributing libraries where the problem of storage has become acute.

The two organizations never duplicate but co-operate closely. The Library is supported by congressional appropriation, but Recording for the Blind relies entirely upon contributions from indivduals and foundations.

The Library's selection of books is made by a committee appointed for that purpose, but Recording for the Blind records at the request of the blind student or his instructor, and will undertake any book that is educational in character.

The books are sent to any one of Recording for the Blind's 14 recording units throughout the country where they are read originally onto tapes by trained volunteers qualified in that field of study. The tapes are then sent to Recording for the Blind headquarters in New York where they are transcribed onto discs. The catalogue lists some 2,300 titles of which the majority are for college undergraduates or adults. Recording for the Blind is, however, producing an increasing number of books for school children and has just completed the recording of 103 books for the State of Connecticut, to be used by blind pupils in grades 4 to 12.

Those who are in contact with the blind should certainly be informed of this useful service and may perhaps want to contribute to its expansion. To use the service, a blind applicant should write direct to Recording for the Blind, 121 East 58th Street, New York 22. He will receive an application blank and a catalogue of books already available. If he wants a book not in the catalogue, he is asked to send the book to Recording for the Blind, which will record it for him and then return the printed copy.

Books in braille and human readers are still of great importance to the blind but recorded books have now become of increasing interest and value. No country in the world offers as complete a service —educational and recreational—as is available here in America.

## Societies

### Wilmer Residents meeting

On the program for the annual meeting of the Wilmer Residents Association held at the Johns Hopkins Hospital, Baltimore, April 7th, 8th and 9th were: "Congenital hereditary stationary corneal dystrophy," A. Edward Maumenee; "Ocular manifestations of the Pierre Robin syndrome," J. Lawton Smith; "Head trauma: II," Frank B. Walsh and David L. Knox; "A major cause of hypotony and its treatment," Paul Chandler and A. Edward Maumenee; "Some aspects of closed-angle glaucoma," Carteret Lawrence; "Closed-angle glaucoma: Pathology studies," Lorenz E. Zimmerman; "Pars planitis: A syndrome of peripheral retinal vitreal opacities and edema of the posterior pole," Robert B. Welch and Henry E. Wahlen; "Corneal scarring due to contact lenses," Charles W. Tillett and Grace M. Tillett; "Some clinical uses of contact lenses," Norris L. Newton; "Indications for therapeutic conjunctival flap," J. Lane Reeves; "Mucormycosis," J. Donald M. Gass; "The relationship of myopia and prematurity," John E. Eisenlohr, Arnall Patz, Paul A. Harper, and Rowland V. Rider; "Displacements of the lens," Angus L. MacLean, "Ocular changes of sickle-cell disease," David Paton; "Ophthalmologist answers today's challenge of reading difficulties of students of all ages," Robert I. Trent and Ernest A. Jones.

"Avian lymphomatosis and uveitis," I. Willard Abrahams; "Effects of T.P.A. on wound healing," Herman K. Goldberg and Maurice E. Langham; "The measurement of aqueous humor formation in human eyes by the suction-cup technique," Maurice E. Langham; "Experimental retinal arterial occlusion," Arnall Patz; "Some practical points on perimetry," Louise Sloan; "Aneurysm cutting optic tract," David B. Clark; "Vascular lesions of the visual cortex with hippocampal gyrus herniations," William Hoyt; "Some aspects of present-day detachment surgery," L. Harrell Pierce; "The effect of intralamellar plastic discs on corneal physiology," William F. Knowles; "Transcorneal potential in vivo," Carl Kupfer; "Isolation of Toxoplasma from human uvea and retina," Leon Jacobs, Marjorie L. Melton, Ronald M. Wood, and Alan C. Woods.

"Tonographic influence of Cyclogyl," Robert A. Schimek and Warren Lieberman; "Enzyme studies on human lenses with primaquine sensitive erythrocytes," William H. Zinkham; "Studies on experimental allergic uveitis," Arthur M. Silverstein and Sylvia Welter; "Ablation of socket after enucleation," Howard A. Naquin; "Further studies on the control of Pseudomonas infection of the cornea," J. Wallace McMeel; "Cataract extraction by tumbling using alpha chymotrypsin, acetylcholine, 8-0 silk sutures," Robert A. Schimek.

"Pseudotumor cerebri syndrome after unilateral radical neck dissection," William G. Marr; "The pathology of circulatory disorders involving the lateral geniculate body," Richard Lindenberg; "Corectopia with midbrain lesions," A. Harry Oleynick and David B. Clark; "Neuro-ophthalmology pathology conference," Richard Lindenberg; "Neuro-ophthalmological clinic," Frank B. Walsh.

### Eye surgery refresher course

The Division of Postgraduate Medical Education, Faculty of Medicine, University of Toronto, presented an "Eye surgery refresher course," on April 4th to 6th. Guest speakers were Dr. Robert J. Brockhurst, Boston, Dr. Graham Clark, New York, and Dr. H. Saul Sugar, Detroit.

On the program for the first session were: Dr. R. Ian Macdonald, "Opening remarks"; Dr. J. C. Hill, "Removal of small lid tumors and repair of lid lacerations"; Dr. Robert J. Brockhurst, "Sugical treatment of vitreous hemorrhages"; Dr. J. C. McCulloch, "The diagnosis and treatment of a leaking wound"; Dr. J. S. Crawford, "Surgical procedure for the correction of ptosis"; Dr. Graham Clark, "The effect of anxiety on wound healing."

The second session was a "Retinal detachment symposium," of which Dr. H. M. Macrae was chairman. Subjects discussed were: "Diagnosis and differential diagnosis," Dr. Brockhurst; "Instrumentation for diagnosis, including indirect and direct ophthalmoscopy and slitlamp examination," Dr. Clark; "Mechanics of the development of retinal detachment and types," Dr. M. Shea; "Factors influencing prognosis," Dr. Brockhurst; "Role of trauma," Dr. Clark; "Diathermy: What is it and what does it do?" Dr. Clark; "Simple diathermy and prophylax-

is," Dr. H. M. Macrae; "Scleral resection," Dr. Shea; "Trap-door procedures" and "Encircling tube," Dr. Brockhurst; "Vitreous implant" and "Light coagulator," Dr. Clark.

On the afternoon of April 5th, Dr. W. R. F. Luke was chairman of the "Symposium on glaucoma." The papers presented were: "Angle-closure glaucoma," Dr. Sugar; "Newer concepts of anatomy of angle drainage systems," Dr. J. S. Speakman; "Clinical tonography," Dr. W. R. F. Luke; "Gonioscopy in glaucoma," and "Techniques of glaucoma surgery (with movies)," Dr. Sugar.

Dr. A. L. Morgan was chairman of the final session at which the following papers were presented: "Transverse myotomies of ocular muscles," Dr. Morgan; "Complications of intraocular surgery and what I have learned from these," Dr. Sugar; "Evisceration," Dr. R. G. C. Kelly; "Ocular signs in trauma," Dr. L. A. Lloyd; "Treatment of amblyopia," Dr. W. P. Callahan.

Preceding the three-day refresher course, a department research meeting was held on Saturday, April 2nd, in the Eye Department of the Toronto General Hospital. The guest of honor was Dr. V. Everett Kinsey, Kresge Eye Institute, Detroit, who spoke on "Recent advances in the etiology of glaucoma." Papers presented by the residents included: Dr. C. B. Mortimer, "Some aspects of the etiology and treatment of congenital cataract"; Dr. R. T. Collyer, "Diabetic retinopathy in juveniles"; Dr. D. E. MacLeod, "The use of heparin in the treatment of macular degeneration"; Dr. W. H. R. Tanner, "Surgical prognosis of two-hour tension curves"; Dr. S. J. Vaile, "Intraocular pseudotumors."

Dr. Nina Morley, Miss Irene Miller, Mrs. A. Lee, and Dr. P. K. Basu, "Growth of corneal cells in tissue culture for biochemical assay": Dr. Nina Morley, Mrs. A. Lee, and Mr. A. Toth, "Measurement of some important metabolites in the cornea"; Dr. J. S. Speakman, "Drainage openings in the trabecular wall and Schlemm's canal; Dr. V. Everett Kinsey, "Research Lecture of Guest of Honor."

Dr. H. R. Hausler and Dr. T. M. Sibay, "Structural details of canal of Schlemm and its emissaries"; Dr. R. K. MacDonald and Dr. T. M. Sibay, "Experimental studies on the aqueous collector channels"; Dr. M. Shea and Dr. S. R. Frankling, "Studies on the effects of intravitreal injection of carrageenan in rabbits"; Dr. W. S. Hunter and Dr. J. C. McCulloch, "The neutralization of cholinesterase inhibition by various oximes."

### Irish Ophthalmological Society

The Irish Ophthalmological Society will hold its annual meeting in Dublin on May 5th, 6th, and 7th. The Montgomery Lecture will be given by Prof. Hans Goldmann of Berne, Switzerland, in Trinity College, Dublin, on Thursday, May 5th.

### Brooklyn Society

Dr. C. Cuppers, Giessen, Germany, spoke on "Pleoptics and its clinical application," at a recent meeting of the Brooklyn Ophthalmological Society.

### Long Island Society

Dr. Richard C. Troutman spoke on "Evaluation of present procedures for enucleation and evisceration," at a recent meeting of the Long Island Ophthalmological Society.

### Oregon Academy

At the ophthalmology sessions of the 19th annual postgraduate convention of the Oregon Academy of Ophthalmology and Otolaryngology held recently in Portland, Dr. Gordon M. Bruce, New York, spoke on "Advances in strabismus surgery," "Rare ocular syndromes," and "Intracranial aneurysms and the eye." Dr. Phillips Thygeson, San Jose, California, discussed: "Corneal ulceration," "Postoperative infections," and "Diagnosis and management of fungus infections in the eye."

Members of the Department of Ophthalmology, University of Oregon, Medical School, headed by Dr. Kenneth C. Swan discussed: "Superior oblique paresis," "Fibrinolysin therapy of acute occlusions of the retinal vessels," "Anatomic approach to the eyelids and lacrimal apparatus," "An approach to the mechanics of postoperative shallow chamber," "Peripheral iridectomy: Some anatomic factors," "Iridectomy through half-lap incision," "A re-evaluation of results of peripheral iridectomy in narrow-angle glaucoma," "Trends in the treatment of ocular neoplasms."

### United Kingdom meeting

The 80th annual congress of the Ophthalmological Society of the United Kingdom was held at the Royal Society of Medicine, 1 Wimpole Street, London, on March 31st and April 1st and 2nd. On the program were:

"Symposium on the management of exophthalmos," held at the Friday afternoon session, with Dr. John Lister, Mr. H. B. Stallard, Mr. Murray Falconer and Mr. T. Keith Lyle as speakers. A group discussion was held on "The problem of the visually defective infant," with Mr. Frank W. Law and Dr. Ronald MacKeith as openers.

Papers included: "Neoplasms of the eyelids," Mr. Dermot Pierse; "The role of corneal microlenses in ophthalmic practice," Mr. H. Treissman; "Some thoughts on asthenopia," Dr. C. R. S. Jackson; "The purposeful use of color," Miss Audrey Mitchell (introduced by Mr. E. C. Glover); " A treatment for dendritic ulcers," Dr. Henry O. Little.

"Opticovegetative reflexes in the pathomechanism of glaucoma," Dr. Paul Weinstien; "Pigmentary glaucoma," Mr. E. S. Perkins; "Peripheral iridectomy in selected cases of glaucoma," Mr. M. H. Luntz; "Peripheral iridectomy for acute glaucoma," Mr. John Primrose; "Factors in the etiology of secondary glaucoma," Mr. C. G. Tulloh.

"The uses of anterior chamber implants," Mr. D. P. Choyce; "Scleral indentation by means of a silver sphere in detachment surgery," Prof. B. Rosengren; "Hydrops of the lid," Mr. J. Ellison; "A study of congenital blepharoptosis," Dr. Ivar Isaksson; "An operation of ptosis," Mr. D. A. Langley; "Trachoma in South Africa," Mr. J. Graham Scott.

### West Virginia academy

The program for the annual meeting of the West Virginia Academy of Ophthalmology and Otolaryngology recently held at the Greenbrier Hotel, White Sulphur Springs, West Virginia, follows: Dr. Harold G. Scheie, Philadelphia, "The surgical management of glaucoma, Part I and Part II"; Dr. Charles E. Iliff, Baltimore, "Adult ocular tumors"; Dr. Oscar T. Becker, Chicago, "Plastic surgery in otolaryngology"; Dr. Helen J. Ossofsky, Washington, D.C., "Pediatric ocular tumors"; Dr. John T. Dickinson, Pittsburgh, "Modern treatment of otosclerosis."

### Wills meeting

The 12th annual clinical conference of the Wills Eye Hospital was recently held at the hospital. There was a total of 428 physicians registered. The informal reception, held on Friday evening at the Barclay Hotel, was attended by 310. A lively interest was displayed in the 37 exhibits of national firms, all of particular interest to the ophthalmologist, covering the newest in pharmaceuticals, optical instruments and surgical appliances.

The hospital rounds on Thursday from 9:00 to 11:00 A.M. were well attended, with informal discussions of the interesting cases by those present. Operative surgery followed.

On Thursday evening, the meeting of the Section on Ophthalmology, College of Physicians, was held at which Dr. Levon K. Garron of Oakland, California, was the guest speaker on the subject of "The trabecular meshwork by electron microscopy." The meeting was preceded by a dinner at the Union League which was very well attended.

The scientific program included 13 scientific presentations by members of the staff and ex-residents of the hospital. The Arthur J. Bedell Lecture was delivered on Saturday morning by Dr. Peter C. Kronfeld, Chicago, on the subject of "The glaucomas secondary to cataract operations." Dr. Kronfeld was introduced by Dr. Roscoe Kennedy, president of the Wills Eye Hospital Society. The Bedell Lecture was enthusiastically received and, at its conclusion, Dr. Kronfeld was presented with a certificate commemorating the event. Tribute was given to Dr. Bedell who was present during the meeting.

The color television program, presented through the courtesy of Smith, Kline and French Laboratories, on Friday and Saturday afternoons, including all types of ocular surgery performed by members of the hospital staff, was excellent. The meeting concluded on Saturday evening with a cocktail and dinner party at the Union League.

### Personal

Dr. Victor C. Rambo, Eye Department, Christian Medical College, Ludhiana, East Punjab, India, has been made a fellow (without examination) of the Royal College of Surgeons, Edinburgh.

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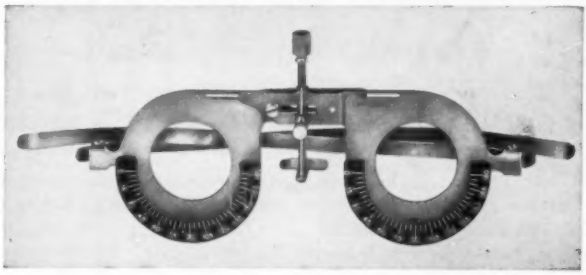

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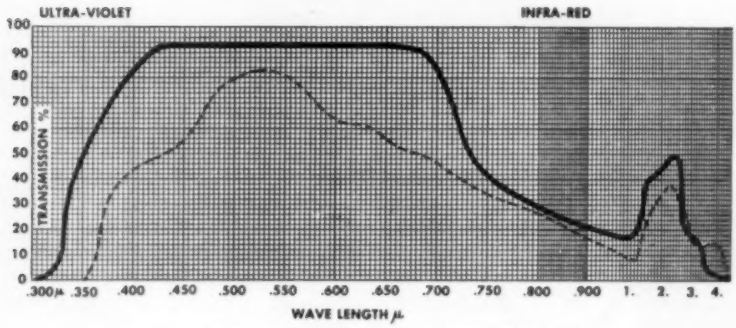


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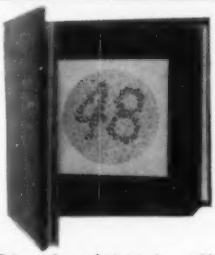


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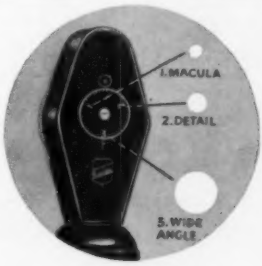


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